# TORONTO NOTES

## 2020



COMPREHENSIVE MEDICAL REFERENCE & REVIEW
FOR MCCQE AND USMLE II

Editors-in-Chief: Sara Mirali & Ayesh Seneviratne
Production Managers: Megan Drupals & Matthaeus Ware

# TORONTO NOTES
# 2020

Comprehensive medical reference and review for the
Medical Council of Canada Qualifying Exam (MCCQE) Part I and
the United States Medical Licensing Exam (USMLE) Step II

36th Edition

Editors-in-Chief:
Sara Mirali and Ayesh Seneviratne

*Wherever the art of medicine is loved,*
*there is also a love of humanity.*

*– Hippocrates*



Toronto Notes for Medical Students, Inc.
Toronto, Ontario, Canada

## Thirty-sixth Edition

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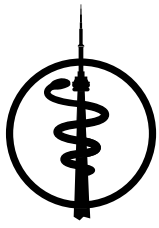
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*and*
*supporters of Toronto Notes*
*who have made the production of the 2020 edition possible!*



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- Save a Child's Heart
- Australian Medical School Association Conference
- Medical Student Research Day
- Ontario Medical Students Weekend (OMSW)
- OMSA's Medical Student Education Research Grant (MSERG)

**Note:**

Many of you have wondered about the *Toronto Notes* logo, which is based on the rod of Asclepius, the Greek god of medicine. The rod of Asclepius consists of a single serpent entwined around a staff. This icon symbolizes both rebirth, by way of a snake shedding its skin, and also authority, by way of the staff.

In ancient Greek mythology, Asclepius was the son of Apollo and a skilled practitioner of medicine who learned the medical arts from the centaur Chiron. Asclepius' healing abilities were so great that he was said to be able to bring back people from the dead. These powers displeased the gods, who punished Asclepius by placing him in the sky as the constellation Orphiuchus.

The rod of Asclepius is at times confused with the caduceus, or wand, of Hermes, a staff entwined with two serpents and often depicted with wings. The caduceus is often used as a symbol of medicine or medical professionals, but there is little historical basis for this symbolism.

As you may have guessed, our logo uses the rod of Asclepius that is modified to also resemble the CN Tower – our way of recognizing the university and community in which we have been privileged to learn the art and science of medicine.

Thomas O'Brien, MD
Class of 2009, M.D. Program, University of Toronto

# Preface – From the Editors

Dear Readers,

As the Editors-in-Chief of *Toronto Notes 2020*, we are proud to present this updated edition.

Toronto Notes began humbly in 1985 from a set of student notes circulated among medical students at the University of Toronto. Over time, Toronto Notes has grown into one of the premier study resources for generations of medical trainees. This rich history solidified our commitment to publish a comprehensive study resource for medical students engaged in clinical rotations and studying for both the Canadian MCCQE Part 1 and the USMLE Step 2.

For the past 36 years, we have remained committed to our original vision. The 2020 edition of Toronto Notes contains significant improvements including:

1. For the first time, Toronto Notes is offered as a 3 book set. We hope this makes our premier study resource more portable for our readers.
2. An improved interactive e-book with high-quality colour images.
3. The clinical handbook is now combined with STAT notes, making it the perfect resource for all of your clinical rotations. The updated handbook also contains a new quick-reference pharmacology table that provides a succinct overview of common drugs, routes of administration, and usage information.
4. Our updated website has been redesigned to complement your studies. Visit us online for our newly updated Colour Atlas, our Radiology Imaging Database, practice review questions, and more.

*Toronto Notes 2020* is produced by Toronto Notes for Medical Students Inc., which is a non-profit organization supporting various charity organizations in Toronto and beyond. This year, Toronto Notes for Medical Students has supported organizations including medical school clubs, community outreach groups, student bursaries and scholarships, and the Canadian Cancer Society. We would like to thank you for supporting these initiatives through your purchase of *Toronto Notes 2020*.

We want to highlight the exceptional work of our team, composed of over 150 medical students, medical illustrators, and faculty members at the University of Toronto Faculty of Medicine. Without the tireless effort expended by these individuals, the production of *Toronto Notes 2020* would not have been possible. In particular, we would like to highlight the amazing work of our executive team, all of whom made personal sacrifices in balancing their clinical and academic duties with the responsibilities asked of them: our production managers, Megan Drupals and Matthaeus Ware, our associate editors, Vanessa Sheng, Jia Tanwani, Calvin Diep, Jagan Sivakumaran, Danielle Jeong, and Nivethan Vela, our EBM editors, Melissa Allwood, Milica Milakovic, Michael Elfassy, Kimia Sheikholeslami, Khizar Karim, and Ryan Wang, our clinical handbook editors, Priya Dhir, Helen Genis, and Meghan Kerr, and our communication managers, Courtney Francis and Shane Natalwalla. Lastly, we would like to thank our partners at Type & Graphics Inc., particularly Enrica Aguilera, for their assistance during the production of *Toronto Notes 2020*.

We hope that *Toronto Notes 2020* enhances your medical knowledge and allows you to perform better on both your clinical rotations and licensing exams. On behalf of the *Toronto Notes 2020* team, we wish you success in your studies and academic endeavours.

Sincerely,

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### Vascular Surgery

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# How to Use This Book

This book has been designed to remain as one book or to be taken apart into smaller booklets. Identify the beginning and end of a particular section, then carefully bend the pages along the perforated line next to the spine of the book. Then tear the pages out along the perforation.

The layout of *Toronto Notes* allows easy identification of important information.
These items are indicated by icons interspersed throughout the text:

| Icon | Icon Name | Significance |
|---|---|---|
|  | Key Objectives | This icon is found next to headings in the text. It identifies key objectives and conditions as determined by the Medical Council of Canada or the National Board of Medical Examiners in the USA. If it appears beside a dark title bar, all subsequent subheadings should be considered key topics. |
|  | Clinical Pearl | This icon is found in sidebars of the text. It identifies concise, important information which will aid in the diagnosis or management of conditions discussed in the accompanying text. |
|  | Memory Aid | This icon is found in sidebars of the text. It identifies helpful mnemonic devices and other memory aids. |
|  | Clinical Flag | This icon is found in sidebars of the text. It indicates information or findings that require urgent management or specialist referral. |
|  | Evidence Based Medicine | This icon is found in sidebars of the text. It identifies key research studies for evidence-based clinical decision making related to topics discussed in the accompanying text. |
|  | Colour Photo Atlas | This icon is found next to headings in the text. It indicates topics that correspond with images found in the Colour Photo Atlas available online (www.torontonotes.ca). |
|  | Radiology Atlas | This icon is found next to headings in the text. It indicates topics that correspond to images found in the Radiology Atlas available online (www.torontonotes.ca). |
|  | Online Resources | This icon is found next to headings in the text. It indicates topics that correspond with electronic resources such as Functional Neuroanatomy or ECGs Made Simple, available online (www.torontonotes.ca). |

## Chapter Divisions

To aid in studying and finding relevant material quickly, each chapter is organized in the following general framework:

**Basic Anatomy/Physiology Review**
- features the high-yield, salient background information students are often assumed to have remembered from their early medical school education

**Common Differential Diagnoses**
- aims to outline a clinically useful framework to tackle the common presentations and problems faced in the area of expertise

**Diagnoses**
- the bulk of the book
- etiology, epidemiology, pathophysiology, clinical features, investigations, management, complications, and prognosis

**Common Medications**
- a quick reference section for review of medications commonly prescribed

# Common Unit Conversions

To convert from the conventional unit to the SI unit, **multiply** by conversion factor

To convert from the SI unit to the conventional unit, **divide** by conversion factor

| | Conventional Unit | Conversion Factor | SI Unit |
|---|---|---|---|
| ACTH | pg/mL | 0.22 | pmol/L |
| Albumin | g/dL | 10 | g/L |
| Bilirubin | mg/dL | 17.1 | μmol/L |
| Calcium | mg/dL | 0.25 | mmol/L |
| Cholesterol | mg/dL | 0.0259 | mmol/L |
| Cortisol | μg/dL | 27.59 | nmol/L |
| Creatinine | mg/dL | 88.4 | μmol/L |
| Creatinine clearance | mL/min | 0.0167 | mL/s |
| Ethanol | mg/dL | 0.217 | mmol/L |
| Ferritin | ng/mL | 2.247 | pmol/L |
| Glucose | mg/dL | 0.0555 | mmol/L |
| HbA1c | % | 0.01 | proportion of 1.0 |
| Hemaglobin | g/dL | 10 | g/L |
| HDL cholesterol | mg/dL | 0.0259 | mmol/L |
| Iron, total | μg/dL | 0.179 | μmol/L |
| Lactate (lactic acid) | mg/dL | 0.111 | mmol/L |
| LDL cholesterol | mg/dL | 0.0259 | mmol/L |
| Leukocytes | x $10^3$ cells/$mm^3$ | 1 | x $10^9$ cells/L |
| Magnesium | mg/dL | 0.411 | mmol/L |
| MCV | $\mu m^3$ | 1 | fL |
| Platelets | x $10^3$ cells/$mm^3$ | 1 | x $10^9$ cells/L |
| Reticulocytes | % of RBCs | 0.01 | proportion of 1.0 |
| Salicylate | mg/L | 0.00724 | mmol/L |
| Testosterone | ng/dL | 0.0347 | nmol/L |
| Thyroxine ($T_4$) | ng/dL | 12.87 | pmol/L |
| Total Iron Binding Capacity | μg/dL | 0.179 | μmol/L |
| Triiodothyronine ($T_3$) | pg/dL | 0.0154 | pmol/L |
| Triglycerides | mg/dL | 0.0113 | mmol/L |
| Urea nitrogen | mg/dL | 0.357 | mmol/L |
| Uric acid | mg/dL | 59.48 | μmol/L |

| | |
|---|---|
| Celsius → Fahrenheit | F = (C x 1.8) + 32 |
| Fahrenheit → Celsius | C = (F – 32) x 0.5555 |
| Kilograms → Pounds | 1 kg = 2.2 lbs |
| Pounds → Ounces | 1 lb = 16 oz |
| Ounces → Grams | 1 oz = 28.3 g |
| Inches → Centimetres | 1 in = 2.54 cm |

# Commonly Measured Laboratory Values

| Test | Conventional Units | SI Units |
|---|---|---|
| ***Arterial Blood Gases*** | | |
| pH | 7.35-7.45 | 7.35-7.45 |
| $PCO_2$ | 35-45 mmHg | 4.7-6.0 kPa |
| $PO_2$ | 80-105 mmHg | 10.6-14 kPa |
| ***Serum Electrolytes*** | | |
| Bicarbonate | 22-28 mEq/L | 22-28 mmol/L |
| Calcium | 8.4-10.2 mg/dL | 2.1-2.5 mmol/L |
| Chloride | 95-106 mEq/L | 95-106 mmol/L |
| Magnesium | 1.3-2.1 mEq/L | 0.65-1.05 mmol/L |
| Phosphate | 2.7-4.5 mg/dL | 0.87-1.45 mmol/L |
| Potassium | 3.5-5.0 mEq/L | 3.5-5.0 mmol/L |
| Sodium | 136-145 mEq/L | 136-145 mmol/L |
| ***Serum Nonelectrolytes*** | | |
| Albumin | 3.5-5.0 g/dL | 35-50 g/L |
| ALP | 35-100 U/L | 35-100 U/L |
| ALT | 8-20 U/L | 8-20 U/L |
| Amylase | 25-125 U/L | 25-125 U/L |
| AST | 8-20 U/L | 8-20 U/L |
| Bilirubin (direct) | 0-0.3 mg/dL | 0-5 μmol/L |
| Bilirubin (total) | 0.1-1.0 mg/dL | 2-17 μmol/L |
| BUN | 7-18 mg/dL | 2.5-7.1 mmol/L |
| Cholesterol | <200 mg/dL | <5.2 mmol/L |
| Creatinine (female) | 10-70 U/L | 10-70 U/L |
| Creatinine (male) | 25-90 U/L | 25-90 U/L |
| Creatine Kinase – MB fraction | 0-12 U/L | 0-12 U/L |
| Ferritin (female) | 12-150 ng/mL | 12-150 μg/L |
| Ferritin (male) | 15-200 ng/mL | 15-200 μg/L |
| Glucose (fasting) | 70-110 mg/dL | 3.8-6.1 mmol/L |
| HbA1c | <6% | <0.06 |
| LDH | 100-250 U/L | 100-250 U/L |
| Osmolality | 275-300 mOsm/kg | 275-300 mOsm/kg |
| ***Serum Hormones*** | | |
| ACTH (0800h) | <60 pg/mL | <13.2 pmol/L |
| Cortisol (0800h) | 5-23 μg/dL | 138-635 nmol/L |
| Prolactin | <20 ng/mL | <20 ng/mL |
| Testosterone (male, free) | 9-30 ng/dL | 0.31-1 pmol/L |
| Thyroxine ($T_4$) | 5-12 ng/dL | 64-155 nmol/L |
| Triiodothyronine ($T_3$) | 115-190 ng/dL | 1.8-2.9 nmol/L |
| TSH | 0.5-5 μU/mL | 0.5-5 μU/mL |
| ***Hematologic Values*** | | |
| ESR (female) | 0-20 mm/h | 0-20 mm/h |
| ESR (male) | 0-15 mm/h | 0-15 mm/h |
| Hemoglobin (female) | 12.3-15.7 g/dL | 123-157 g/L |
| Hemoglobin (male) | 13.5-17.5 g/dL | 140-174 g/L |
| Hematocrit (female) | 36-46% | 36-46% |
| Hematocrit (male) | 41-53% | 41-53% |
| INR | 1.0-1.1 | 1.0-1.1 |
| Leukocytes | 4.5-11 x $10^3$ cells/$mm^3$ | 4.5-11 x $10^9$ cells/L |
| MCV | 88-100 $\mu m^3$ | 88-100 fL |
| Platelets | 150-400 x $10^3/mm^3$ | 150-400 x $10^9$/L |
| PTT | 25-35 s | 25-35 s |
| Reticulocytes | 0.5-1.5% of RBC | 20-84 x $10^9$/L |

# ELOM Ethical, Legal, and Organizational Medicine

**Anna Kurdina** and **David Wiercigroch,** chapter editors
**Vanessa Sheng** and **Jaya Tanwani,** associate editors
**Melissa Allwood** and **Milica Milakovic,** EBM editors
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Further information on these topics can be found in the Objectives of the Considerations of the Legal, Ethical and Organizational Aspects of the Practice of Medicine (CLEO) – which can be downloaded free of charge from the Medical Council of Canada website at http://mcc.ca/wp-content/uploads/CLEO.pdf.

There are three main types of law in Canada: criminal, civil, and administrative. The penalties for violating each are, in general, as follows: criminal - fine or incarceration; civil - monetary damages paid to the wronged party; and administrative - sanctions by the regulator (such as a suspension by the College of Physicians and Surgeons). All three types of law can be engaged by a single act. For example, a physician that inappropriately touches a patient can be liable for criminal (sexual assault), civil (monetary damages paid to the patient for the civil wrong of sexual assault), and administrative (fines and sanctions up to and including loss of ability to practice medicine for sexual abuse) penalties.

Canadian law applicable to medical practice varies between jurisdictions and changes over time.

Criminal law is nationwide, but civil and administrative law varies between provinces and territories. This section is meant to serve only as a guide. Students and physicians should ensure that their practices conform to local and current laws.

# Acronyms

| | |
|---|---|
| AE | adverse event |
| ART | advanced reproductive technologies |
| CFMS | Canadian Federation of Medical Students |
| CFPC | College of Family Physicians of Canada |
| CMA | Canadian Medical Association |
| CME | continuing medical education |
| CMPA | Canadian Medical Protective Association |
| CPSO | College of Physicians and Surgeons of Ontario |
| EMR | electronic medical record |
| FMEQ | Fédération médicale étudiante du Québec |
| FRCPC | Fellow of the Royal College of Physicians of Canada |
| FRCSC | Fellow of the Royal College of Surgeons of Canada |
| GA | gestational age |
| GDP | gross domestic product |
| HCCA | Health Care Consent Act |
| IVF | in vitro fertilization |
| LMCC | Licentiate of the Medical Council of Canada |
| MCC | Medical Council of Canada |
| OECD | Organization for Economic Co-operation and Development |
| OMA | Ontario Medical Association |
| OTC | over the counter |
| PHO | Provincial Housestaff Organization |
| PIPEDA | Personal Information Protection and Electronic Documents Act |
| POA | power of attorney |
| PTMA | Provincial/Territorial Medical Association |
| RCPSC | Royal College of Physicians and Surgeons of Canada |
| RDoC | Resident Doctors of Canada |
| SDM | substitute decision-maker |

# The Canadian Health Care System

## Overview of Canadian Health Care System

- one federal, three territorial, and ten provincial systems
- major complexities in establishment of Canadian health policy include geographical diversity, socioeconomic divisions, and international pressures
- financed by both the public (70%) and private (30%) sectors
- each provincial plan must cover all medically necessary health services delivered in hospitals and by physicians; may choose to cover services such as home care and prescription drugs
- non-insured health services and fees are either covered by private insurance or by the individual
- workers' compensation funds cover treatment for work-related injuries and diseases

**Table 1. Division of Government Responsibilities in Health Care**

| Federal Government | Provincial Government |
|---|---|
| Health care services for Indigenous people, federal government employees (RCMP and armed forces), immigrants, and civil aviation personnel | Establishment, maintenance and management of hospitals, asylums, charities, and charitable institutions (*Constitution Act*, 1867) |
| Marine hospitals and quarantine (*Constitution Act*, 1867) | Licensing of physicians, nurses, and other health professionals |
| Investigations into public health | Determining the standards for licensing all hospitals |
| Regulation of food and drugs | Administering provincial medical insurance plans |
| Inspection of medical devices | Financing health care facilities |
| Administration of health care insurance | Delivery of certain public health services |
| General information services related to health conditions and practices | |
| Role in health derived from government's constitutional powers over criminal law (basis for legislation such as *Food and Drugs Act and Controlled Substances Act*), spending, bioterrorism, and 'peace, order, and good government' | |

**Principles of the Canada Health Act**

1. Public Administration: provincial health insurance programs must be administered by public authorities
2. Comprehensiveness: provincial health insurance programs must cover all necessary diagnostic, physician, and hospital services
3. Universality: all eligible residents must be entitled to health care services
4. Portability: emergency health services must be available to Canadians who are outside their home province, paid for by the home province
5. Accessibility: user fees, charges, or other obstructions to insured health care services are not permitted

## Legal Foundation

The legal foundation of the Canadian health system is based on:

- two constitutional documents:
  1. ***Constitution Act*** (1867): deals primarily with the jurisdictional power between federal and provincial governments
  2. ***The Canadian Charter of Rights and Freedoms*** (1982): does not guarantee a right to health care, but given government's decision to finance health care, they are constitutionally obliged to do so consistently with the rights and freedoms outlined in the Charter (including the right to equality, physicians' mobility rights, etc.)
- two statutes:
  1. ***Canada Health Act*** (1984): outlines the national terms and conditions that provincial health systems must meet in order to receive federal transfer payments
  2. ***Canada Health and Social Transfer Act*** (1996): federal government gives provinces a single grant for health care, social programs, and post-secondary education; division of resources at provinces' discretion

The federal government can reduce its contributions to provinces that violate the key principles of the *Canada Health Act*

# History of the Canadian Health Care System

1867 *British North America Act* (now *Constitution Act*) establishes Canada as a confederacy
- "establishment, maintenance, and management of hospitals" under provincial jurisdiction

1965 *Royal Commission on Health Services* (Hall Commission) recommends federal leadership and financial support with provincial government operation

1984 *Canada Health Act* passed by federal government
- replaces *Medical Care Act* (1966) and *Hospital Insurance and Diagnostic Services Act* (1957)
- provides federal funds to provinces with universal hospital insurance
- maintains federal government contribution at 50% on average, with poorer provinces receiving more funds
- medical insurance must be "comprehensive, portable, universal, and publicly administered"
- bans extra-billing by new fifth criterion: accessibility

1996 *Canada Health and Social Transfer Act* passed by federal government
- federal government gives provinces a single grant for health care, social programs, and post-secondary education; division of resources at provinces' discretion

2001 *Kirby and Romanow Commissions* appointed

*Kirby Commission* (final report, October 2002)
- examines history of health care system in Canada, pressures and constraints of current health care system, role of federal government, and health care systems in foreign jurisdictions

*Romanow Commission* (final report, November 2002)
- dialogue with Canadians on the future of Canada's public health care system

2004 *First Ministers' Meeting on the Future of Health Care* produces a 10 year plan
- priorities include reductions in waiting times, development of a national pharmacare plan, and primary care reform

2005 *Chaoulli v. Québec*, Supreme Court of Canada decision
- rules that Québec's banning of private insurance is unconstitutional under the *Québec Charter of Rights*, given that patients do not have access to those services under the public system in a timely way

2011 First progress report by the Health Council reviews progress (2004 First Ministers' 10 year plan)
- significant reductions in wait times for specific areas (such as cancer, joint replacement, and sight restoration), but may have inadvertently caused increases in wait times of other services
- despite large investments into EMRs, Canada continues to have very low uptake, ranking last in the *Commonwealth Fund International Health Policy* survey, with only 37% use among primary care physicians
- little progress in creating a national strategy for equitable access to pharmaceuticals; however, there has been some success in increasing pharmacists' scope of practice, reducing generic drug costs, and implementing drug information systems
- increases in funding to provinces at 6% per annum until the 2016-2017 fiscal year; from then onwards, increases tied to nominal GDP at a minimum of 3% per annum

2012 Second progress report by the Health Council reviews progress towards 2004 First Ministers' 10 year plan
- funding is sufficient; however, more innovation is needed including incentivizing through models of remuneration
- 46 recommendations made to address the lack of progress

2014 Expiry of current 10 Year Health Care Funding Agreement between federal and provincial governments
- *Canadian Doctors for Refugee Care v. Canada*, the Federal Court of Canada ruled that the federal government could not significantly reduce/eliminate healthcare services for refugee claimants as to do so would constitute "cruel and unusual treatment" contrary to the Charter of Rights and Freedoms

2015 Negotiations underway for a new Health Accord with a $3 billion investment over four years to homecare and mental health services by the elected Liberal government

2017 New 10 year Canada Health Accord reached with a $11.5 billion federal investment over 10 years to homecare and mental health services and a 3% annual rise in the Canada Health Transfer (down from 6% in the previous agreement) by the elected Liberal government

2019 The federal government announced the creation of a national drug agency. It will negotiate prices on behalf of Canada's drug plans, assess the effectiveness of prescription drugs, and develop a national formulary

# Health Care Expenditure and Delivery in Canada

- the projected total health care expenditure in 2018 is expected to reach $253.5 billion, comprising 11.3% of the GDP, or approximately $6839 CDN per person

### Sources of Health Care Funding

- 69% of total health expenditure in 2018 came from public-sector funding with 65% coming from the provincial and territorial governments, and another 5% from other parts of the public sector: federal direct government, municipal, and social security funds. 31% is from private sources including out of pocket (16%), private insurance (12%), and other (3%)
- public sector covers services offered on either a fee for service, capitation, or alternate payment plan in physicians' offices and in hospitals
- public sector does not cover services provided by privately practicing health professionals (e.g. dentists, chiropractors, optometrists, massage therapists, osteopaths, physiotherapists, podiatrists, psychologists, private duty nurses, and naturopaths), prescription drugs, OTC drugs, personal health supplies, and use of residential care facilities

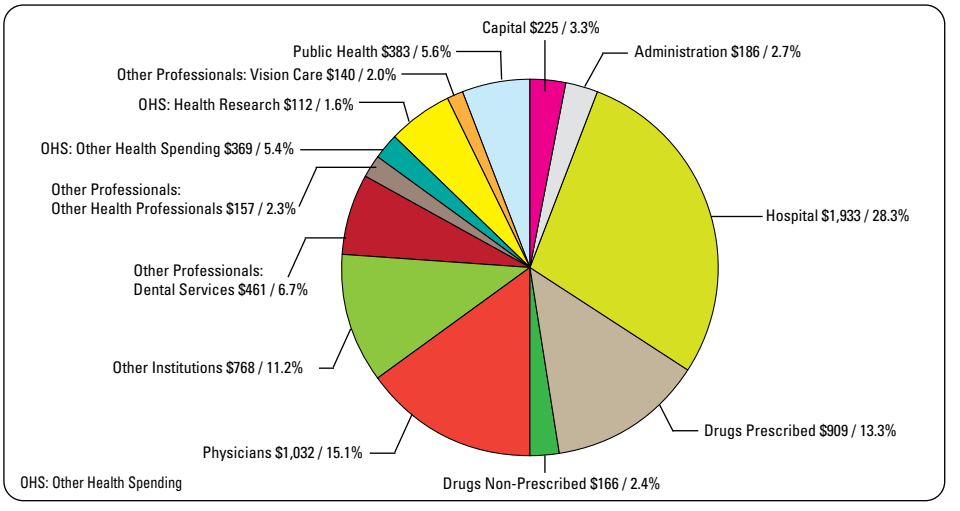



**Figure 1. Total health expenditure per capita by use of funds, Canada 2018** (dollars and percentage share)
Adpated from source: National Health Expenditure Database, Canadian Institute for Health Informaton

### Delivery of Health Care

- hospital services in Canada are publicly funded but delivered through private, not-for-profit institutions owned and operated by communities, religious organizations, and regional health authorities
- other countries, such as the United States (a mix of public and private funding, as well as private for-profit and private not-for-profit delivery), and the United Kingdom (primarily public funding and delivery) have different systems of delivery

# Physician Licensure and Certification

**Table 2. Key Physician Certification and Licensing Bodies in Canada**

| Certifying Body | Description |
|---|---|
| **MCC** | Certifies physicians with the LMCC. LMCC acquired by passing the MCC Qualifying Examination Parts I and II |
| **RCPSC** | Certifies specialists who complete an accredited residency program and pass the appropriate exam |
| | Voluntary membership of the RCPSC is designated FRCPC or FRCSC |
| **CFPC** | Certifies family physicians who complete an accredited residency program and pass the Certification Examination in Family Medicine |
| **Licensing Body** | 13 provincial medical regulatory (licensing) authorities |
| | All postgraduate residents and all practicing physicians must hold an educational or practice license from the licensing body in the province in which they study or practice |
| **CPSO** | Membership to the provincial licensing authority is mandatory |
| | Licensing authority functions include: |
| | Provide non-transferable licensure to physicians |
| | Maintaining ethical, legal, and competency standards and developing policies to guide doctors |
| | Investigating complaints against doctors |
| | Disciplining doctors guilty of professional misconduct or incompetence |
| | At times of license investiture and renewal, physicians must disclose if they have a condition (such as HIV positivity, drug addiction, or other illnesses) that may impact their ability to practice safely |

- physician certification is governed nationally, while the medical profession in Canada self-regulates under the authority of provincial legislation
- self-regulation is based on the premise that due to the advanced education and training involved in the practice of medicine, the lay person is not in a position to accurately judge the standards of the profession; the self-regulating colleges have a mandate to regulate the profession in the public interest
- the RCPSC and CFPC are responsible for monitoring ongoing CME and professional development
- certification by the LMCC plus either the RCPSC or CFPC is a minimum requirement for licensure by most provincial licensing authorities

## Role of Professional Associations

**Table 3. Key Professional Associations**

| Association | Description |
|---|---|
| **CMA** | Provides leadership to doctors and advocates for access to high quality care in Canada |
| | Represents physician and population concerns at the national level |
| | Membership is voluntary |
| **OMA and Other PTMAs** | Negotiates fee and benefit schedules with provincial governments |
| | Represents the economic and professional interests of doctors |
| | Membership is voluntary |
| **CMPA** | Physician-run organization that protects the integrity of member physicians |
| | Provides legal defence against allegations of malpractice or negligence |
| | Provides risk management and educational programs |
| | Membership is voluntary |
| **RDoC and PHO** | Upholds economic and professional interests of residents across Canada |
| | Facilitates discussion amongst PHOs regarding policy and advocacy items |
| **CFMS and FMÉQ** | Medical students are represented at their universities by student bodies, which collectively form the CFMS or FMÉQ |
| | FMÉQ membership includes that of francophone medical schools |

# Ethical and Legal Issues in Canadian Medicine

## Introduction to the Principles of Ethics



- ethics addresses:
  1. principles and values that help define what is morally permissible or not
  2. rights, duties, and obligations of individuals and groups
- the practice of medicine assumes there is one code of professional ethics for all doctors and that they will be held accountable by that code and its implications
- the doctor-patient relationship is formed on trust, which is recognized in the concept of fiduciary duty/responsibility of physician towards patient
- a fiduciary duty is a legal duty to act in another party's interest. Profit from the fiduciary relationship must be strictly accounted for with any improper profit (monetary or otherwise) resulting in sanctions against the physician and potentially compensation to the patient, even if no harm has befallen the patient

**Table 4. The Four Principles Approach to Medical Ethics**

| Principle | Definition |
|---|---|
| **Autonomy** | Recognizes an individual's right and ability to decide for themselves according to their beliefs and values |
| | May not be applicable in situations where informed consent and choice are not possible or may not be appropriate |
| **Beneficence** | Patient values-based best interests standard that combines doing good, avoiding harm, considering the patient's values, beliefs, and preferences, so far as these are known |
| | Autonomy should be integrated with the physician's conception of a patient's medically-defined best interests |
| | Aim is to minimize harmful outcomes and maximize beneficial ones |
| | Paramount in situations where consent/choice is not possible or may not be appropriate |
| **Non-Maleficence** | Obligation to avoid causing harm; primum non nocere ("First, do no harm") |
| | Limit condition of the Beneficence principle |
| **Justice** | Fair distribution of benefits and harms within a community, regardless of geography or income |
| | Concept of fairness: Is the patient receiving what they deserve – their fair share? Are they treated the same as equally situated patients? (equity) How does one set of treatment decisions impact others? (equality) |
| | Equality and equity are different notions of justice. Equality is distribution of resources to all irrespective of needs, and equity is distribution of resources based on unique needs. Both concepts raise different considerations |
| | Basic human rights, such as freedom from persecution and the right to have one's interests considered and respected |



**Autonomy vs. Competence vs. Capacity**
**Autonomy**: the right that patients have to make decisions according to their beliefs and preferences
**Competence**: the ability to make a specific decision for oneself as determined legally by the courts
**Capacity**: the ability to make a specific decision for oneself as determined by clinicians

### CMA Code of Ethics

- the CMA developed a Code of Ethics that acts as a common ethical framework for Canadian physicians
- the Code of Ethics is:
  - prepared by physicians for physicians and applies to physicians, residents, and medical students
  - based on the fundamental ethical principles of medicine
  - sources include the Hippocratic Oath, developments in human rights, recent bioethical discussion
  - CMA policy statements address specific ethical issues not mentioned by the code (e.g. abortion, transplantation, and euthanasia)

The **CMA Code of Ethics and Professionalism** is a quasi-legal standard for physicians; if the law sets a minimal moral standard for doctors, the Code augments these standards

## Confidentiality

### Overview of Confidentiality

- when determining legal and ethical issues surrounding patient information, start from the point that all information given by the patient is both confidential (meaning it cannot be disclosed to others) and privileged (meaning it cannot be used in court), then determine whether exceptions to this exist
- the legal and ethical basis for maintaining confidentiality is that a full and open exchange of information between patient and physician is central to a therapeutic relationship
- privacy is the right of patients (which they may forego), while confidentiality is the duty of doctors (which they must respect barring patient consent or the requirements of the law)
- if inappropriately breached by a doctor, physician can be sanctioned by the hospital, court, or regulatory authority
- based on the ethical principle of patient autonomy, patients have the right to the following:
  - control of their own information
  - the expectation that information concerning them will receive proper protection from unauthorized access by others (see *Privacy of Medical Records*, ELOM7)
- confidentiality may be ethically and legally breached in certain circumstances (e.g. the threat of harm to others)
  - while physician-patient privilege exists, it is less strong than solicitor-client privilege. Physicians can tell patients that they will only disclose their information where it is mandated by law and that these exceptions are generally quite narrow. Physicians should avoid promising absolute confidentiality or privilege, as it cannot be guaranteed
- physicians should seek advice from their local health authority or the CMPA before disclosing HIV status of a patient to someone else
  - many jurisdictions make mandatory not only the reporting of serious communicable diseases (e.g. HIV), but also the reporting of those who harbour the agent of the communicable disease
  - physicians failing to abide by such regulations could be subject to professional or civil actions
- legal duty to maintain patient confidentiality is imposed by provincial health information legislation and precedent-setting cases in the common law

**Legal Aspects of Confidentiality**
Advice should always be sought from provincial licensing authorities and/or legal counsel when in doubt

**CMA Code of Ethics and Professionalism**
"Fulfill your duty of confidentiality to the patient by keeping identifiable patient information confidential; collecting, using, and disclosing only as much health information as necessary to benefit the patient; and sharing information only to benefit the patient and within the patient's circle of care. Exceptions include situations where the informed consent of the patient has been obtained for disclosure or as provided for by law"

**Reasons to Breach Confidentiality**

- Child abuse
- Fitness to drive
- Communicable disease
- Coroner report
- Duty to inform/warn

### Statutory Reporting Obligations

- legislation has defined specific instances where public interest overrides the patient's right to confidentiality; varies by province, but may include:
  1. suspected child abuse or neglect – report to local child welfare authorities (e.g. Children's Aid Society)
  2. fitness to drive a vehicle or fly an airplane – report to provincial Ministry of Transportation (see Geriatric Medicine, GM11)
  3. communicable diseases – report to local public health authority (see Public Health and Preventive Medicine, PH26)
  4. improper conduct of other physicians or health professionals – report to College or regulatory body of the health professional (sexual impropriety by physicians is required reporting in some provinces)
  5. vital statistics must be reported; reporting varies by province (e.g. in Ontario, births are required to be reported within 30 d to Office of Registrar General or local municipality; death certificates must be completed by a MD then forwarded to municipal authorities)
  6. reporting to coroners (see *Physician Responsibilities Regarding Death*, ELOM16)
- physicians who fail to report in these situations are subject to prosecution and penalty, and may be liable if a third party has been harmed

### Duty to Protect/Warn

- the physician has a duty to protect the public from a known dangerous patient; this may involve taking appropriate clinical action (e.g. involuntary detainment of violent patients for clinical assessment), informing the police, or warning the potential victim(s) if a patient expresses an intent to harm
- first established by a Supreme Court of California decision in 1976 (*Tarasoff v. Regents of the University of California*)
- Canadian courts have not expressly imposed a mandatory duty to report, however, the CMA Code of Ethics and some provincial/territorial regulatory authorities may oblige physicians to report (mandatory reporting rather than permissive)
- concerns of breaching confidentiality should not prevent the MD from exercising the duty to protect; however, the disclosed information should not exceed that required to protect others

**Ontario's Medical Expert Panel on Duty to Warn**
1998;158(11):1473-1479

- There should be a duty to inform when a patient reveals that they intend to do serious harm to another person(s) and it is more likely than not that the threat will be carried out
- Where a threat is directed at a person or group and there is a specific plan that is concrete and capable of commission and the method for carrying it out is available to the threatener, the physician should immediately notify the police and, in appropriate circumstances, the potential victim. The report should include the threat, the situation, the physician's opinion, and the information upon which it is based

- applies in a situation where:
  1. there is an imminent risk
  2. to an identifiable person or group
  3. of serious bodily harm or death

### Disclosure for Legal Proceedings
- disclosure of health records can be compelled by a court order, warrant, or subpoena

### Privacy of Medical Records
- privacy of health information is protected by professional codes of ethics, provincial and federal legislation, the *Canadian Charter of Rights and Freedoms*, and the physician's fiduciary duty
- the federal government created the PIPEDA in 2000 which established principles for the collection, use, and disclosure of information that is part of commercial activity (e.g. physician practices, pharmacies, private labs)
- PIPEDA has been superseded by provincial legislation in many provinces, such as the *Ontario Personal Health Information Protection Act*, which applies more specifically to health information

**CMA Code of Ethics and Professionalism**
- Protect the health information of your patients
- Provide information reasonable in the circumstances to patients about the reasons for the collection, use, and disclosure of their health information
- Be aware of your patients' rights with respect to the collection, use, disclosure, and access to their health information; ensure that such information is recorded accurately

### Duties of Physicians with Regard to the Privacy of Health Information
- inform patients of information-handling practices through various means (e.g. posting notices, brochures and pamphlets, and/or through discussions with patients)
- obtain the patient's expressed consent to disclose information to third parties
  - under Ontario privacy legislation, the patient's expressed consent need not be obtained to share information between health care team members involved in the "circle of care." However, the patient may withdraw consent for this sharing of information and may put parts of the chart in a "lock box"
    - physicians have a professional obligation to facilitate timely transmission of the patient's medical record to third parties (with the patient's consent), such as for insurance claims. Failure to do so has resulted in sanctions by regulatory bodies
    - while patients have a right of access to their medical records, physicians can charge a "reasonable fee" commensurate with the time and material used in providing copies/access
- provide the patient with access to their entire medical record; exceptions include instances where there is potential for serious harm to the patient or a third party
- provide secure storage of information and implement measures to limit access to patient records
- ensure proper destruction of information that is no longer necessary
- regarding taking pictures or videos of patients, findings, or procedures, in addition to patient consent and privacy laws, trespassing laws apply in some provinces
- CPSO published policy is designed to help Ontario physicians understand legal and professional obligations set out under the *Regulated Health Professions Act, 1991, the Medicine Act, 1991*, and *the Personal Health Information Protection Act, 2004*. This includes regulations regarding express or implied consent, incapacity, lock boxes, disclosure under exceptional circumstances, mandatory reporting, ministry audits, subpoenas, court orders and police, as well as electronic records and voice messaging communications: http://www.cpso.on.ca/Policies-Publications/Policy/Confidentiality-of-Personal-Health-Information
- it is the physician's responsibility to ensure appropriate security provisions with respect to electronic records and communications
  - with the advent of digital records, there have been increasing issues with access of healthcare providers that are not part of the patient's circle of care accessing medical records inappropriately (e.g. curiousity or for profit). All staff should be aware that most EMRs log which healthcare providers view records and automatically flag files for further review in certain cases (e.g. same surname, VIP patients, audit of access to records)

**Lock Boxes**
The term "lock boxes" applies to situations where the patient has expressly restricted their physician from disclosing specific aspects of their health information to others, even those involved in the patient's circle of care. Note that the *Personal Health Information Protection Act* (PHIPA) provisions denote that patients may not prevent physicians from disclosing personal health information permitted/required by the law

## Consent and Capacity

### Ethical Principles Underlying Consent and Capacity
- consent is the autonomous authorization of a medical intervention by a patient
- usually the principle of respect for patient autonomy must be balanced by the principle of beneficence
- where a patient cannot make an autonomous decision (i.e. incapable), it is the duty of the SDM (or the physician in an emergency) to act on the patient's known prior wishes or, failing that, to act in the patient's best interests
- there is a duty to discover, if possible, what the patient would have wanted when capable
- central to determining best interests is understanding the patient's values, beliefs, and patient's interpretation of cultural or religious background
- more recently expressed wishes take priority over remote ones
- patient wishes may be verbal or written
- patients found incapable to make a specific decision should still be involved in that decision as much as possible; this is known as assent
- agreement or disagreement with medical advice does not determine findings of capacity/incapacity
- however, patients opting for care that puts them at risk of serious harm that most people would want to avoid should have their capacity carefully assessed. Steer clear from tendency to define what reasonable person standard may be. If appropriate, look to discern patterns of justification offered by patient and how they interpret their values, beliefs and culture/religion

**CPSO Policy Consent**
Obtaining valid consent before carrying out medical, therapeutic, and diagnostic procedures has long been recognized as an elementary step in fulfilling the doctor's obligations to the patient

## Four Basic Requirements of Valid Consent

**1. Voluntary**
- consent must be given free of coercion or pressure (e.g. from parents or other family members who might exert 'undue influence')
- the physician must not deliberately mislead the patient about the proposed treatment

**2. Capable**
- the patient must be able to understand and appreciate the nature and effect of their condition as well as of the proposed treatment or decision

**3. Specific**
- the consent provided is specific to the procedure being proposed and to the provider who will carry out the procedure (e.g. the patient must be informed if students will be involved in providing the treatment)

**4. Informed**
- sufficient information and time must be provided to allow the patient to make choices in accordance with their wishes, including:
  - the nature of the treatment or investigation proposed and its expected effects
  - all significant risks and special or unusual risks
  - alternative treatments or investigations and their anticipated effects and significant risks
  - the consequences of declining treatment
  - answers to any questions the patient may have
  - the reasonable person test – the physician must provide all information that would be needed "by a reasonable person in the patient's position" to be able to make a decision
  - disclose common adverse events and all serious risks (e.g. death), even if remote
  - it is the physician's responsibility to make reasonable attempts to ensure that the patient understands the information, including overcoming language barriers, or communication challenges
  - physicians have a duty to inform the patient of all legitimate therapeutic options and must not withhold information based on conscientious objections (e.g. not discussing the option of emergency contraception)

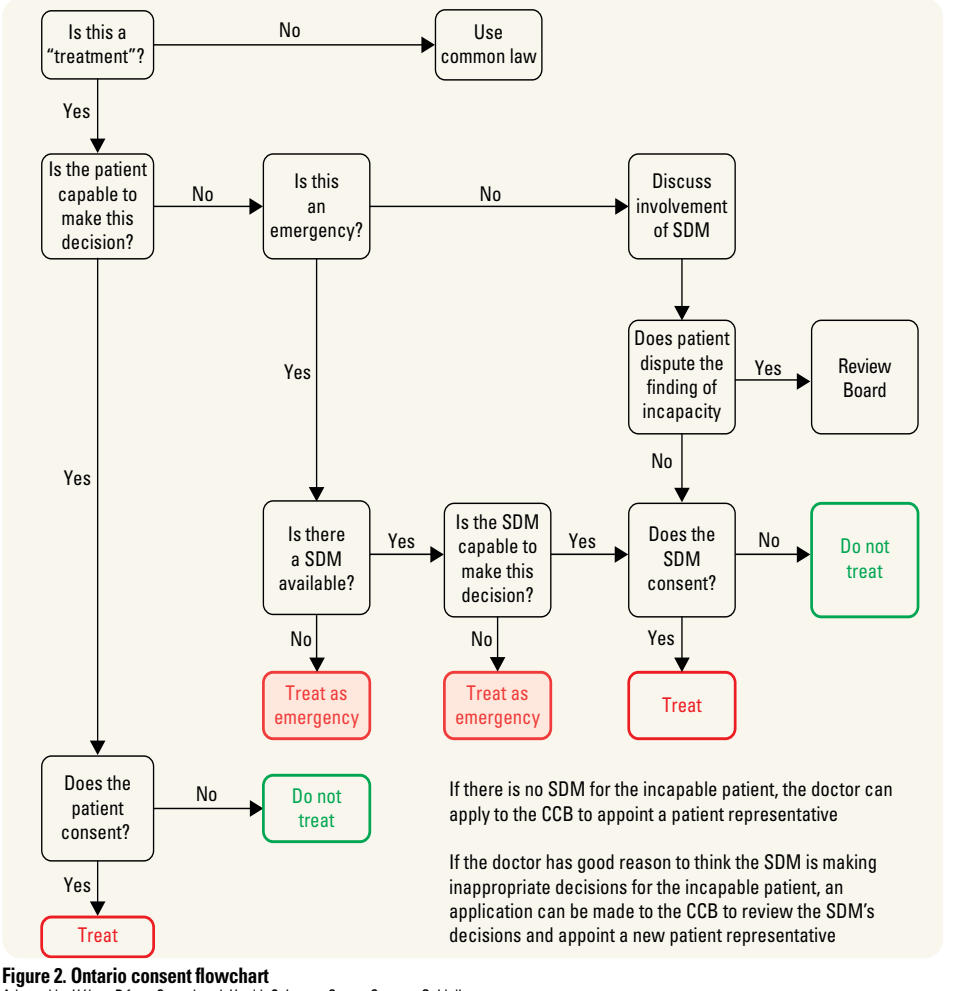



**Figure 2. Ontario consent flowchart**
Adapted by Hébert P from Sunnybrook Health Sciences Centre Consent Guidelines

**4 Basic Elements of Consent**
- Voluntary
- Capable
- Specific
- Informed

**Professional Considerations**

**Elderly Patient**
- Identify their goals of care and resuscitation options (CPR or DNR), if applicable
- Check for documentation of advance directives and POA where applicable

**Pediatric Patient**
- Identify the primary decision-maker (parents, guardian, wards-of-state, emancipated)
- Regarding capacity assessment see *Pediatric Aspects of Capacity*, ELOM11
- Be wary of custody issues if applicable

**Terminally Ill or Palliative Patient**
- Consider the SPIKES approach to breaking bad news
- What are patient's goals of care (i.e. disease vs. symptom management)?
- Identify advance directives, POA, or SDM, if applicable (see ELOM10)
- Check for documentation of resuscitation options (CPR or DNR) and likelihood of success

**Incapable Patient**
- If not already present, perform a formal capacity assessment and thoroughly document
- Identify if the patient has an SDM or who has their POA
- Check the patient's chart for any Mental Health Forms (e.g. Form 1) or any forms they may have on their person (e.g. Form 42)

**Criteria For Administration of Treatment for an Incapable Patient in Emergency Situations**
- Patient is experiencing extreme suffering
- Patient is at risk of sustaining serious bodily harm if treatment is not administered promptly (loss of life or limb)

Patients may also ask to waive the right to choice (e.g. "You know what's best for me, doctor") or delegate their right to choose to someone else (e.g. a family member)

This is not necessarily only in emergency situations. Patients may choose to exercise relational autonomy i.e. conception of self-determination where decisions are made considering relationships and person's social supports. The patient is still in the centre, but chooses to involve others in the decision

## Obtaining Legal Consent

- consent of the patient must be obtained before any medical intervention is provided; consent can be:
  - verbal or written, although written is usually preferred
  - a signed consent form is only evidence of consent – it does not replace the process for obtaining valid consent
  - most important component is what the patient understands and appreciates, not what the signed consent form states
  - implied (e.g. a patient holding out their arm for an immunization) or expressed
- consent is an ongoing process and can be withdrawn or changed after it is given, unless stopping a procedure would put the patient at risk of serious harm
  - if consent has been withdrawn during a procedure, the MD must stop treatment unless stopping the procedure would threaten the patient's life
  - in obtaining consent to continue the procedure, the physician need only re-explain the procedure and risks if there has been a material change in circumstances since obtaining consent originally. If there has been no material change in circumstances, simple assent to continue is sufficient (*Ciarlariello v. Schachter*)
- HCCA of Ontario (1996) covers consent to treatment, admission to a facility, and personal assistance services (e.g. home care)



The Supreme Court of Canada expects physicians to disclose the risks that a "reasonable" person would want to know. In practice, this means disclosing minor risks that are common as well as serious risks that happen infrequently, especially those risks that are particularly relevant to a particular patient (e.g. hearing loss for a musician)

## Exceptions to Consent

**1. Emergencies**

- treatment can be provided without consent where a patient is experiencing severe suffering, or where a delay in treatment would lead to serious harm or death and consent cannot be obtained from the patient or their SDM
- emergency treatment should not violate a prior expressed wish of the patient (e.g. a signed Jehovah's Witness card)
- if patient is incapable, MD must document reasons for incapacity and why situation is emergent
- patients have a right to challenge a finding of incapacity as it removes their decision-making ability
- if a SDM is not available, MD can treat without consent until the SDM is available or the situation is no longer emergent

**2. Legislation**

- mental health legislation allows for:
  - the detention of patients without their consent
  - psychiatric outpatients may be required to adhere to a care plan in accordance with Community Treatment Orders
  - Public Health legislation allows medical officers of health to detain, examine, and treat patients without their consent (e.g. a patient with TB refusing to take medication) to prevent transmission of communicable diseases

**3. Special Situations**

- public health emergencies (e.g. an epidemic or communicable disease treatment)
- warrant for information by police



**Major Exceptions to Consent**
- Emergencies
- Public and Mental Health Legislation
- Communicable diseases

## Consequences of Failure to Obtain Valid Consent

- treatment without consent is battery (an offense in tort), even if the treatment is life-saving (excluding situations outlined in *Exceptions to Consent*)
- treatment of a patient on the basis of poorly informed consent may constitute negligence, also an offense in tort
- the onus of proof that valid consent was not obtained rests with the plaintiff (usually the patient)



**Consent**
- Treatment without consent = battery, including if NO consent or if WRONG procedure
- Treatment with poor or invalid consent = negligence

## Overview of Capacity

- capacity is the ability to:
  - understand information relevant to a treatment decision
  - appreciate the reasonably foreseeable consequences of a decision or lack of a decision
- capacity is specific for each decision (e.g. a person may be capable to consent to having a chest x-ray, but not for a bronchoscopy)
- capacity can change over time (e.g. temporary incapacity secondary to delirium)
- most Canadian jurisdictions distinguish capacity to make healthcare decisions from capacity to make financial decisions; a patient may be deemed capable of one, but not the other
- a person is presumed capable unless there is good evidence to the contrary
- capable patients are entitled to make their own decisions
- capable patients can refuse treatment even if it leads to serious harm or death; however, decisions that put patients at risk of serious harm or death require careful scrutiny



**CPSO Policy on Capacity**
Capacity is an essential component of valid consent, and obtaining valid consent is a policy of the CMA and other professional bodies

## Assessment of Capacity

- capacity assessments must be conducted by the clinician providing treatment and, if appropriate, in consultation with other healthcare professionals (e.g. another physician, a mental health nurse)
- clinical capacity assessment may include:
  - specific capacity assessment (i.e. capacity specific to the decision at hand):
    1. effective disclosure of information and evaluation of patient's reason for decision
    2. understanding of:
       - their condition
       - the nature of the proposed treatment



**Capacity Assessment**
Test for understanding: can the patient recite what you have disclosed?
Test for appreciation: are their beliefs responsive to evidence?
Refer to: JAMA The Rational Clinical Examination "Does This Patient Have Medical Decision-Making Capacity?"

  - alternatives to the treatment
  - the consequences of accepting and rejecting the treatment
  - the risks and benefits of the various options
3. for the appreciation needed for decision-making capacity, a person must:
  - acknowledge the symptoms that affect them
  - be able to assess how the various options would affect them
  - be able to reach a decision, and make a choice, not based primarily upon delusional belief
- general impressions
- input from psychiatrists, neurologists, etc. for any underlying mental health or neurological condition that may affect insight or decision-making
- employ "Aid to Capacity Evaluation" or any other capacity assessment tool/guideline
- a decision of incapacity may warrant further assessment by psychiatrist(s), legal review boards (e.g. in Ontario, the Consent and Capacity Review Board), or the courts
- if found incapable by the Consent and Capacity Review Board, patient must receive notice of their ability to pursue judicial review (and essentially appeal the determination)

### Treatment of the Incapable Patient in a Non-Emergent Situation
- obtain informed consent from SDM
- an incapable patient can only be detained against their will to receive treatment if they meet criteria for certification under the *Mental Health Act* (see Psychiatry, PS53); in such a situation:
  - document assessment in chart
  - notify patient of assessment using appropriate Mental Health Form(s) (Form 42 in Ontario)
  - notify Rights Advisor

### Substitute Decision-Makers
- SDMs must follow the following principles when giving informed consent:
  - act in accordance with wishes previously expressed by the patient while capable
  - if wishes unknown, act in the patient's best interest, taking the following into account:
    1. values and beliefs held by the patient while capable
    2. whether well-being is likely to improve with vs. without treatment
    3. whether the expected benefit outweighs the risk of harm
    4. whether a less intrusive treatment would be as beneficial as the one proposed
- the final decision of the SDM may and should be challenged by the MD if the MD believes the SDM is not abiding by the above principles

### Instructional Advance Directives
- allow patients to exert control over their care once they are no longer capable
- the patient sets out their decisions about future health care, including who they would allow to make treatment decisions on their behalf and what types of interventions they would want
- takes effect once the patient is incapable with respect to treatment decisions
- in Ontario, a person can appoint a power of attorney for personal care to carry out their advance directives
  - the legal threshold to appoint a Power of Attorney for personal care is intentionally set lower than the legal threshold for capacity to consent to many complex medical treatments. This allows a patient that lacks treatment capacity to appoint a person of their choosing to make the decision for them
- patients should be encouraged to review these documents with their family and physicians and to reevaluate them often to ensure they are current with their wishes

## POWERS OF ATTORNEY
- all Guardians and Attorneys have fiduciary duties for the dependent person

### Definitions
- **Power of Attorney for Personal Care**
  - a legal document in which one person gives another the authority to make personal care decisions (health care, nutrition, shelter, clothing, hygiene, and safety) on their behalf if they become mentally incapable
- **Guardian of the Person**
  - someone who is appointed by the Court to make decisions on behalf of an incapable person in some or all areas of personal care, in the absence of a POA for personal care
- **Continuing Power of Attorney for Property**
  - legal document in which a person gives another the legal authority to make decisions about their finances if they become unable to make those decisions
- **Guardian of Property**
  - someone who is appointed by the Public Guardian and Trustee or the Courts to look after an incapable person's property or finances
- **Public Guardian and Trustee**
  - acts as a SDM of last resort on behalf of mentally incapable people who do not have another individual to act on their behalf



**Aid to Capacity Evaluation**
J Gen Intern Med 1999;14(1):27-34
- Ability to understand the medical problem
- Ability to understand the proposed treatment
- Ability to understand the alternatives (if any) to the proposed treatment
- Ability to understand the option of refusing treatment or of it being withheld or withdrawn
- Ability to appreciate the reasonably foreseeable consequences of accepting the proposed treatment
- Ability to appreciate the reasonably foreseeable consequences of refusing the proposed treatment
- Ability to make a decision that is not substantially based on delusions or depression



Most provinces have legislated hierarchies for SDMs; the hierarchy in Ontario is:
- Legally appointed guardian
- Appointed attorney for personal care, if a power of attorney confers authority for treatment consent (see Powers of Attorney)
- Representative appointed by the Consent and Capacity Board
- Spouse or common law partner
- Child (age 16 or older) or parent (unless the parent has only a right of access)
- Parent with only a right of access
- Sibling
- Other relative(s)
- Public guardian and trustee



**Other Types of Capacity Not Covered by the HCCA**
- Testamentary (ability to make a will)
- Fitness (ability to stand trial)
- Financial (ability to manage property – Form 21 of the *Mental Health Act*)
- Personal (ability to care for oneself on a daily basis)
- Substitute consent for a procedure whose primary purpose is research, sterilization for non-therapeutic purposes, or removal of organs or tissue for transplantation (does not apply to those already declared dead)

- **Pediatric Aspects of Capacity Covered**
  - no age of consent in all provinces and territories except Québec; consent depends on patient's decision-making capacity
  - Québec has a specific age of consent, but common law and case law deem underage legal minors capable, allowing these individuals to make their own choices
  - infants and children are assumed to lack mature decision-making capacity for consent but they should still be involved (i.e. be provided with information appropriate to their comprehension level)
  - adolescents are usually treated as adults
  - preferably, assent should still be obtained from patient, even if not capable of giving consent
  - in the event that the physician believes the SDM is not acting in the child's best interests, an appeal must be made to the local child welfare authorities
  - under normal circumstances, parents have right of access to the child's medical record



There is no age of consent in Ontario
Capacity is assessed on an individual basis

# Negligence



Errors of care are compatible with non-negligent care if they are ones that a reasonably cautious and skilled MD could make (i.e. mistakes can be made due to 'honest error')



**Four Basic Elements for Action Against a Physician to Succeed in Negligence**

1. A duty of care owed to the patient (i.e. doctor/patient relationship must be established)
2. A breach of the duty of care
3. Some harm or injury to the patient
4. The harm or injury must have been caused by the breach of the duty of care

### Ethical Basis

- the doctor-patient relationship is formed on trust, which is recognized in the concept of fiduciary duty/responsibility of physician towards patient
- negligence or malpractice is a form of failure on the part of the physician in fulfilling their fiduciary duty in providing appropriate care and leading to harm of the patient (and/or abuse of patient's trust)

### Legal Basis

- physicians are legally liable to their patients for causing harm (tort) through a failure to meet the standard of care applicable under the circumstances
- standard/duty of care is defined as one that would reasonably be expected under similar circumstances of an ordinary, prudent physician of the same training, experience, specialization, and standing
- liability arises from physician's common law duty of care to their patients in the doctor/patient relationship (or, in Québec, from the Civil Code provisions regarding general civil liability)
- action(s) in negligence (or civil liability) against a physician must be launched by a patient within a specific prescribed period required by the respective province in which the actions occurred

# Truth-Telling





**CPSO Policy on Truth-Telling**
Physicians should provide patients with whatever information that will, from the patient's perspective, have a bearing on medical decision-making and communicate that information in a way that is comprehensible to the patient



**Examples of Warning of Impending Bad News**
"I have something difficult to tell you…"
"This may come as a shock to you, but the tests indicate…"
"There is no easy way for me to tell you this, so I will tell you straight away that you have a serious problem…"



**Adverse Event**
An unintended injury or complication from health care management resulting in disability, death, or prolonged hospital stay

### Ethical Basis

- helps to promote and maintain a trusting physician-patient relationship
- patients have a right to be told important information that physicians have regarding their care
- enables patients to make informed decisions about health care and their lives

### Legal Basis

- required for valid patient consent (see *Consent and Capacity*, ELOM7)
  - goal is to disclose information that a reasonable person in the patient's position would need in order to make an informed decision ("standard of disclosure")
- withholding information can be a breach of fiduciary duty and duty of care
- obtaining consent on the basis of misleading information can be seen as negligent

### Evidence about Truth-Telling

- it is a patient's right to have the option of knowing what is wrong with them
- most patients want to know what is wrong with them
- although many patients want to protect family members from bad news, they themselves would want to be informed in the same situation
- truth-telling improves adherence and health outcomes
- informed patients are more satisfied with their care and most often take the news better than expected
- negative consequences of truth-telling can include decreased emotional well-being, anxiety, worry, social stigmatization, and loss of insurability

### Challenges in Truth-Telling

**Medical Error**

- medical error may be defined as 'preventable adverse events (AEs)' caused by the patient's medical care and not the patient's underlying illness; some errors may be identified before they harm the patient, so not all error is truly 'adverse'
- many jurisdictions and professional associations expect and require physicians to disclose medical error; that is, any event that harms or threatens to harm patients must be disclosed to the patient or the patient's family and reported to the appropriate health authorities
- physicians must disclose to patients the occurrence of AEs or errors caused by medical management, but should not suggest that they resulted from negligence because:
  - negligence is a legal determination
  - error is not equal to negligence

- disclosure allows the injured patient to seek appropriate corrective treatment promptly
- physicians should avoid simple attributions as to cause and sole responsibility of others or oneself
- physicians should offer apologies or empathic expressions of regret (e.g. "I wish things had turned out differently") as these build trust and are not admissions of guilt or liability
- Apology Acts across Canada protect apologies, both as expressions of regret and admissions of responsibility, from being used as evidence of liability and negligence



**Open Disclosure of AEs: Transparency and Safety in Health Care**
Surg Clin North Am 2012;92(1):163-177
Health care providers have a fiduciary duty to disclose AEs to their patients. Professional societies codify medical providers' ethical requirement to disclose AEs to patients in accordance with the four principles of biomedical ethics. Transparency and honesty in relationships with patients create opportunities for learning that lead to systems improvements in health care organizations. Disclosure invariably becomes a component of broad systems improvement and is closely linked to improving patient safety.

### Breaking Bad News

- 'bad news' may be any information that reveals conditions or illnesses threatening the patient's sense of well-being
- poorly done disclosure may be as harmful as non-disclosure
  - caution patients in advance of serious tests and disclose possible bad findings
  - give time for patient to reflect prior to receiving such news
  - give warnings of impending bad news by reviewing prior discussions
  - provide time for the patient and questions
  - adequate supports and strategies should always be provided following disclosure of difficult news
- **SPIKES** protocol was developed to facilitate "breaking bad news"
  - **S**ETTING and LISTENING SKILL
  - Patient **P**ERCEPTIONS of condition and seriousness
  - **I**NVITATION from patient to receive information
  - **K**NOWLEDGE - provide medical facts
  - Explore **E**MOTIONS and **E**MPATHIZE
  - **S**TRATEGY and **S**UMMARY



**Truth-Telling in Discussing Prognosis in Advanced Life-Limiting Illnesses**
Palliat Med 2007;21(6):507-517
**Purpose**: To examine truth telling in discussing prognosis in patients with progressive advanced life-limiting illnesses and their caregivers.
**Methods**: Systematic review of studies of any design evaluating communication of prognostic information that included adult patients with advanced, life-limiting illnesses, their caregivers and qualified health care professionals (HCPs).
**Results**: 46 eligible studies were identified. While most HCPs believed that patients and caregivers should be told the truth about prognosis, many avoid the topic or withhold information, possibly due to perceived lack of training, stress, no time to attend to emotional needs, fear of negatively impacting the patient, uncertainty about prognostication, requests from family members, and a feeling of inadequacy or hopelessness regarding unavailability of curative treatments.
**Conclusion**: Truth-telling regarding prognosis in advanced life-limiting illnesses is poor by HCPs, likely related to multiple personal limitations, professional demands and perceptions regarding impact on the patient and caregivers.

### Arguments Against Truth-Telling

- may go against certain cultural norms and expectations
- may lead to patient harm, but only in extreme, rare situations
- medical uncertainty may result in the disclosure of uncertain or inaccurate information

### Exceptions to Truth-Telling

- a patient may waive their right to know the truth about their situation (i.e. decline information that would normally be disclosed) when:
  - the patient clearly declines to be informed
  - a strong cultural component exists that should be respected and acknowledged
  - the patient may wish others to be informed and make the medical decisions for them
- the more weight for the consequences for the patient from non-disclosure, the more carefully one must consider the right to ignorance
- 'emergencies': an urgent need to treat may legitimately delay full disclosure; the presumption is that most people would want such treatment and the appropriate SDM cannot be found
- 'therapeutic privilege'
  - withholding of information by the clinician in the belief that disclosure of the information would itself lead to severe anxiety, psychological distress, or physical harm to the patient
  - clinicians should avoid invoking therapeutic privilege due to its paternalistic overtones; it is a defence of non-disclosure that is rarely accepted anymore
  - it is often not the truth that is unpalatable; it is how it is conveyed that can harm the patient

## Ethical Issues in Health Care

### Managing Controversial and Ethical Issues in Practice

- discuss in a non-judgmental manner
- ensure patients have full access to relevant and necessary information
- identify if certain options lie outside the physician's moral boundaries and refer to another physician if appropriate
- consult with appropriate ethics committees or boards
- protect freedom of moral choice for students or trainees

## Reproductive Technologies

### Overview of the Maternal-Fetal Relationship

- in general, maternal and fetal interests align
- in some situations, a conflict between maternal autonomy and the best interests of the fetus may arise



The fetus does not have legal rights until it is born alive and with complete delivery from the body of the woman

### Ethical Issues and Arguments

- principle of reproductive freedom: women have the right to make their own reproductive choices
- coercion of a woman to accept efforts to promote fetal well-being is an unacceptable infringement of her personal autonomy

## Legal Issues and Arguments

- the law protects a woman's right to life, liberty, and security of person, and does not recognize fetal rights; key aspects of the mother's rights include:
  - if a woman is competent and refuses medical advice, her decision must be respected even if the fetus will suffer
  - the fetus does not have legal rights until it is born alive and with complete delivery from the body of the woman
  - a pregnant woman that is addicted to teratogenic substances cannot be detained and treated to protect the fetus (*Winnipeg Child and Family Services (Northwest Area) v. G. (D.F.), [1997] 3 S.C.R. 925*)
  - a fetus is not a "human being" within the meaning of the Criminal Code of Canada, thus medical negligence during delivery resulting in the death of a fetus that has not been born alive does not constitute criminal negligence causing death (manslaughter) and cannot attract criminal penalties (*R v Sullivan*)

*Royal Commission on New Reproductive Technologies* (1993) recommendations:

1. medical treatment must never be imposed upon a competent pregnant woman against her wishes
2. no law should be used to confine a pregnant woman in the interest of her fetus
3. the conduct of a pregnant woman in relation to her fetus should not be criminalized
4. child welfare should never be used to control a woman's behaviour during pregnancy
5. civil liability should never be imposed upon a woman for harm done to her fetus during pregnancy

Examples involving the use of established guidelines

- a woman is permitted to refuse HIV testing during pregnancy, even if vertical transmission to fetus results, however, once the baby is born, breastfeeding and even theoretical transmission of HIV may attract criminal liability (this area of law is unsettled)
- a woman is permitted to refuse Caesarean section in labour that is not progressing, despite evidence of fetal distress

## Advanced Reproductive Therapies

- includes non-coital insemination, hormonal ovarian stimulation, and IVF
- topics with ethical concerns:
  - donor anonymity vs. child-centred reproduction (i.e. knowledge about genetic medical history)
  - preimplantation genetic testing for diagnosis before pregnancy
  - use of new techniques without patients appreciating their experimental nature
  - embryo status – the Supreme Court of Canada maintains that fetuses are "unique" but not persons under law; this view would likely apply to embryos as well
  - access to ART
  - private vs. public funding of ART
  - social factors limiting access to ART (e.g. same-sex couples)
  - the 'commercialization' of reproduction

## Fetal Tissue

- pluripotent stem cells can currently be derived from human embryonic and fetal tissue
- potential uses of stem cells in research
  - studying human development and factors that direct cell specialization
  - evaluating drugs for efficacy and safety in human models
  - cell therapy: using stem cells grown in vitro to repair or replace degenerated/destroyed/malignant tissues (e.g. Parkinson's disease)
  - genetic treatment aimed at altering somatic cells (e.g. myocardial or immunological cells) is acceptable and ongoing

## Induced Abortion

- CMA definition of induced abortion: the active termination of a pregnancy before fetal viability (fetus >500 g or >20 wk GA)
- CMA policy on induced abortion
  1. induced abortion should not be used as an alternative to contraception
  2. counselling on contraception must be readily available
  3. full and immediate counselling services must be provided in the event of unwanted pregnancy
  4. there should be no delay in the provision of abortion services
  5. no patient should be compelled to have a pregnancy terminated
  6. physicians should not be compelled to participate in abortion – if morally opposed, the physician should inform the patient so she may consult another physician
  7. no discrimination should be directed towards either physicians who do not perform or assist at induced abortions or physicians who do
  8. induced abortion should be uniformly available to all women in Canada and health care insurance should cover all the costs (note: the upper limit of GA for which coverage is provided varies between provinces)
  9. elective termination of pregnancy after fetal viability may be indicated under exceptional circumstances



**Neonate as Member of Society**
Paediatr Child Health 2012;17(8):443-444

- Once outside the mother's body, the neonate becomes a member of society with all the rights and protections other vulnerable persons receive.
- Non-treatment of a neonate born alive is only acceptable if <22 wk GA
- 23-25 wk GA: treatment should be a consensual decision between physician and parents
- 25 wk GA and more: neonate should receive full treatment unless major anomalies or conditions incompatible with life are present



**Advanced Reproductive Technologies: Ethically Appropriate Actions**

- Educate patients and address contributors to infertility (e.g. stress, alcohol, medications, etc.)
- Investigate and treat underlying health problems causing infertility
- Wait at least 1 yr before initiating treatment with ART (exceptions – advanced age or specific indicators of infertility)
- Educate and prepare patients for potential negative outcomes of ART



Payment of gamete donors is currently illegal in Canada. The ART Act is currently not being enforced as it does not clarify whether ART falls under the jurisdiction of the federal or provincial government



**Semen Regulations of the Food and Drug Act, 1996**
No one under age 18 can donate sperm or eggs, except for the purpose of creating a child that the donor plans to raise himself/herself (e.g. young patients receiving radiation therapy for cancer that may cause infertility)



**Assisted Human Reproduction Act, 2004**
Surrogate mothers cannot be paid or offered compensation beyond a reimbursement of their expenses

### Ethical and Legal Concerns and Arguments
- in Canada, there is no criminal prohibition regarding abortion
- it is a woman's medical decision to be made in consultation with whom she wishes; there is no mandatory role for spouse/family
- 2nd and even 3rd trimester abortions are not illegal in Canada, but are usually only carried out when there are serious risks to the woman's health, or if the fetus has died in utero or has major malformations (e.g. anencephaly). Medical termination of pregnancy (MTP) for social reasons are now conducted in select medical centres in Canada

### Prenatal/Antenatal Genetic Testing
- uses
  1. to confirm a clinical diagnosis
  2. to detect genetic predisposition to a disease
  3. allows preventative steps to be taken and helps patient prepare for the future
  4. gives parents the option to terminate a pregnancy or begin early treatment
- ethical dilemmas arise because of the sensitive nature of genetic information; important considerations of genetic testing include:
  - the individual and familial implications
  - its pertinence to future disease
  - its ability to identify disorders for which there are no effective treatments or preventive steps
  - its ability to identify the sex of the fetus
  - ethical issues and arguments regarding the use of prenatal/antenatal genetic testing include:
    - obtaining informed consent is difficult due to the complexity of genetic information
    - doctor's duty to maintain confidentiality vs. duty to warn family members
    - risk of social discrimination (e.g. insurance) and psychological harm

### Legal Aspects
- no current specific legislation exists
- testing requires informed consent
- no standard of care exists for clinical genetics, but physicians are legally obligated to inform patients that prenatal testing exists and is available
- a physician may be able to breach confidentiality in order to warn family members about a condition if harm can possibly be prevented via treatment or prevention. In general, the patient's consent is required, unless the harm to be avoided is sufficiently serious to rise to the level of imminent risk of serious bodily harm or death (i.e. not a chronic condition, but an acute life-threatening condition)

### Genetic Testing: Ethically Appropriate Actions
- thorough discussion and realistic planning with patient before testing is done
- genetic counselling for delivery of complex information

**The Tri-Council Policy Statement**
1. Genetic treatment aimed at altering germ cells is prohibited in Canada and elsewhere
2. Embryo research is permitted up to 14 d post-fertilization
3. Embryos created for reproductive purposes that are no longer required may be used
4. Gamete providers must give free and informed consent for research use
5. No commercial transactions in the creation and use of the embryos are permitted
6. Creation of embryos solely for research purposes is prohibited
8. Human cloning is strictly prohibited
8. Risks of coercion must be minimized (i.e. the fertility treatment team may not be pressured to generate more embryos than necessary)
9. One may only discuss the option of using fetal tissue for research after free and informed choice to have a therapeutic abortion has been made by the patient
10. Physicians responsible for fertility treatment may not be part of a stem cell research team

## End-of-Life Care

### Overview of Palliative and End-of-Life Care
- focus of care is comfort and respect for person nearing death and maximizing quality of life for patient, family, and loved ones
  - palliative care is an approach that improves the quality of life of patients facing life-threatening illness, through the prevention and relief of suffering, including treating pain, physical, psychosocial, and spiritual concerns
- appropriate for any patient at any stage of a serious or life-limiting illness
- may occur in a hospital, hospice, in the community, or at home
- often involves an interdisciplinary team of caregivers
- addresses the medical, psychosocial, and spiritual dimensions of care

**Palliative Care – Not the Same As Euthanasia**
Palliative care is an approach designed to improve symptoms and quality of life for the duration of a person's life, but unlike Medical Assistance in Dying, it does not aim directly at or intend to end the person's life. Many palliative care physicians are incorporating MAID into their practice, though some may conscientiously object

### Euthanasia and Medical-Assistance in Dying (MAID)
- euthanasia: knowingly and intentionally performing an act, with or without consent, that is explicitly intended to end another person's life where that person has an incurable illness
- medical-assistance in dying: the administering or prescribing for self-administration, by a medical practitioner or nurse practitioner, of a substance, at the request of a person, that causes their death
  - palliative sedation: the use of sedative medications for patients that are terminally ill to relieve suffering and manage symptoms. Though the intent is not to hasten death, this may be a foreseeable consequence
  - withdrawing or withholding life sustaining interventions (e.g. artificial ventilation or nutrition) that are keeping the patient alive but no longer wanted or indicated

**MAID: Ethically Appropriate Actions**
- Respect capable decisions to forgo treatment
- Provide appropriate palliative measures
- Try to assess reasons for such requests from patients to see if there are 'reversible factors' (such as depression, pain, loneliness, anxiety) that can be treated

### Common Ethical Arguments/Opinions
- criminally prohibiting assistance in death, forces some who will eventually become too unwell to end their own lives at an earlier time and forces others to endure intolerable suffering.
- patient has the right to make autonomous choices about the time and manner of their own death
- belief that there is no ethical difference between the acts of euthanasia/assisted suicide and forgoing life-sustaining treatments
- belief that these acts benefit terminally ill patients by relieving suffering

- patient autonomy has limits
- death should be the consequence of the morally justified withdrawal of life-sustaining treatments only in cases where there is a fatal underlying condition, and it is the condition (not the withdrawal of treatment) that causes death
- an argument presented in the Carter case (see below) suggested permitting MAID will detract support for palliative care, since with proper palliative care, the number of requests for MAID would decrease. This argument was rejected in *Carter v. Canada*, as making people suffer to potentially improve care for others is not acceptable

### Legal Aspect

- in the *Carter v. Canada* decision of February 2015, the criminal prohibition on assistance in suicide was ruled unconstitutional to the extent that they prohibit physician-assisted death for a competent adult person who (1) clearly consents to the termination of life and (2) has a grievous and irremediable medical condition that causes enduring suffering that is intolerable to the individual in the circumstances of his or her condition
- Bill C-14 (June 17, 2016) legalized MAID by amending the Criminal Code to create exemptions permitting medical practitioners to provide MAID, specified the eligibility criteria, safeguards, and required documentation and authorization from the Minister of Health, as well as new offences for failure to comply with the new regulations. http://www.parl.ca/DocumentViewer/en/42-1/bill/C-14/royal-assent
  - as the Bill C-14 criteria are narrower than the Carter decision, there are ongoing constitutional challenges to the MAID framework as it currently stands

### Bill C-14 Criteria for MAID

- patient is eligible for publicly-funded health services in Canada
- at least 18 yr of age, and has capacity for clear and freely given consent
- grievous and irremediable medical condition: in an advanced state of irreversible decline in capability
- suffering intolerable to the patient, not relieved under conditions they consider acceptable
- natural death is reasonably foreseeable

MAID Process

1. eligibility criteria satisfied
2. patient signs and dates a written request for MAID
3. two independent witness sign the written request. Witnesses must be 18 years of age, understand the nature of MAID, and must not a) benefit (financially or otherwise) from the death, b) be an owner or operator of the healthcare facility where the patient is receiving care, c) be directly involved in the provision of health or personal care of the patient
4. HCP must inform the patient that they can withdraw their consent at any time
5. two independent assessors (MD or NP) must provide written confirmation that eligibility criteria are met
6. 10 clear days must elapse between the request and the day on which MAID is provided, unless both healthcare providers agree that a shorter period is appropriate due to the patient's imminent death or loss of capacity
7. throughout the 10 d period and immediately before providing MAID, the HCP must give the individual an opportunity to withdraw the request and ensure that the patient gives express consent to receive MAID
   - contravention of this process is an offence punishable by up to five years in prison

### Acceptable Use of Palliative and End-of-Life Care

- the use of palliative sedation with opioids in end-of-life care, knowing that death may occur as an unintended consequence (principle of double effect) is distinguished from euthanasia and assisted suicide where death is the primary intent
- the appropriate withdrawal of life-support is distinguished from euthanasia and assisted suicide as it is seen as allowing the underlying disease to take its 'natural course', but this distinction may be more theoretical than real
- consent for withdrawal of life-support must be sought from the capable patient, or in case of incapable patient the SDMs, as per the *Health Care Consent Act* and *Substitute Decisions Act*, and as re-affirmed by the ruling in *Cuthbertson v. Rasouli* in 2013, as palliative care would be instituted and consent for that would require SDM consent
- refusals of care by the patient that may lead to death as well as requests for a hastened death, ought to be carefully explored by the physician to rule out any 'reversible factors' (e.g. poor palliation, depression, poverty, ill-education, isolation) that may be hindering authentic choice
- Government of Canada – Services and Information for End-of-Life Care: https://www.canada.ca/en/health-canada/topics/end-life-care.html
  - options and decision making at end of life: palliative care, do not resuscitate orders, refusal or withdrawal of treatment, refusal of food and drink, palliative sedation, MAID
  - decisions at end of life: informed and capacity for consent, substitute decision maker, advanced care planning (written plan, will, or medical directive) often established through a family meeting



**Mental Health Outcomes of Family Members of Patients Who Request Physician Aid in Dying**
J Pain Symptom Manage 2009;38(6):807-815
**Purpose**: To describe how patients' end-of-life choices affected family caregivers of Oregonians who requested aid in dying and to assess degree of grief, use of mental health services and depression amongst family caregivers.
**Methods**: Family members of Oregonian patients who had explicitly requested aid in dying (including those whose loved ones received a lethal prescription and those whose loved ones died by lethal ingestion) were surveyed. For comparison purposes, family members of patients who died of cancer or amyotrophic lateral sclerosis also were surveyed.
**Results**: 95 family members were surveyed, including 59 of those whose loved ones received a lethal prescription and 36 whose loved ones died by lethal ingestion. Among those whose family member requested aid in dying, whether or not the patient accessed a lethal prescription had no influence on subsequent depression, grief, or mental health services use; however, family members of patients who received a lethal prescription were more likely to believe that their loved one's choices were honored and less likely to have regrets about how the loved one died. Comparing family members of those who requested aid in dying to those who did not revealed no differences in primary mental health outcomes of depression, grief, or mental health services use. Family members of patients who requested aid in dying felt more prepared and accepting of the death than comparison family members.
**Conclusion**: Pursuit of aid in dying does not have negative effects on surviving family members and may be associated with greater preparation and acceptance of death.

### Physician Responsibilities Regarding Death

- physicians are required by law to complete a medical certificate of death unless the coroner needs notification; failure to report death is a criminal offence
- *Coroner's Act*, 1990 (specific to Ontario, similar in other provinces) requires physicians to notify a coroner or police officer if death occurs:
  - due to violence, negligence, misconduct, misadventure, or malpractice
  - during pregnancy or is attributable to pregnancy
  - suddenly and unexpectedly
  - from disease which was not treated by a legally qualified medical practitioner
  - from any cause other than disease
  - under suspicious circumstances
  - death from MAID
- coroner investigates these deaths, as well as deaths that occur in psychiatric institutions, jails, foster homes, nursing homes, hospitals to which a person was transferred from a facility, institution or home, etc.
- in consultation with forensic pathologists and other specialists, the coroner establishes:
  - the identity of the deceased
  - where and when the death occurred
  - the medical cause of death
  - the means of death (i.e. natural, accidental, suicide, homicide, or undetermined)
- coroners do not make decisions regarding criminality or legal responsibility
- while the Supreme Court of Canada noted that nothing in the *Carter v. Canada* decision compelled a physician to participate in MAID, the College of Physicians and Surgeons of Ontario mandatory referral policy, which has been upheld by the courts, requires physicians in Ontario to provide an effective referral if the physician conscientiously objects to MAID
  - the impact of MAID on religious institutions' obligation towards patients is not yet clear

**Notify Coroner if Death Occurs due to:**
- Violence, negligence, misconduct
- Pregnancy
- Sudden or unexpected causes
- Disease not treated
- Cause other than disease
- Suspicious circumstances
- MAID

## Physician Competence and Professional Conduct

### CanMEDS Competencies (Ethical/Policy Statement)

- a framework of professional competencies established by the Medical Council of Canada (MCC) as objectives for the MCC Qualifying Exam
- further information on Medical Council of Canada objectives can be found at www.mcc.ca

**CanMeds Competencies**
- Communicator
- Collaborator
- Health Advocate
- Leader
- Professional
- Scholar
- Medical Expert

### Legal Considerations

- physicians' conduct and competence are legally regulated to protect patients and society via mandatory membership to provincial governing bodies (e.g. the CPSO)
- physicians are legally required to maintain a license with the appropriate authority, and are thus legally bound to outlined policies on matters of conduct within their medical practice
- the ultimate constraint on MD behaviour with regards to unprofessionalism is 'conduct unbecoming a physician', such as inappropriate behaviour with colleagues, conflicts of interest, untruthfulness, unethical billing practices, and sexual impropriety with patients

**CPSO Policy: Ending the Physician-Patient Relationship**
Discontinuing services that are needed is an act of professional misconduct unless done by patient request, alternative services are arranged, or adequate notice has been given

### Common Policies on Physician Conduct

- physicians must ensure that patients have access to continuous on-call coverage and are never abandoned
  - physicians are required to comply with the law, which include human rights laws. A failure to accommodate a disability in violation of human rights legislation, can result in the regulatory body sanctioning the physician in addition to any penalties assigned by the human rights tribunal
- sexual conduct with patients, even when consented to by the patient, is a serious matter that can lead to accusations of battery by the patient and provincial governing body. Important notes on this topic include:
  - inappropriate sexual conduct includes intercourse, undue touching, references to sexual matters, sexual jokes, and physician presence when capable patients undress or dress
  - in specified situations, physicians may have a personal relationship with a patient provided a year has passed since the last therapeutic contact
  - physicians are permanently prohibited from personal relationships with patients whom they saw for psychotherapy
  - in Ontario, physicians must report any colleagues of whom they have information regarding sexual impropriety (as per CPSO Code of Ethics)
- physicians must maintain adequate records for each patient, which include:
  - demonstration that care has been continuous and comprehensive
  - minimal standards for record-keeping, including readability, diagnosis, differential diagnosis, appropriate tests and referrals, and a coherent patient record, including drugs, a cumulative patient profile, and all aspects of charting that are required for safe patient care (full standards available at www.cpso.on.ca). Another physician should be able to take over the safe care of the patient based on the record
  - records stored for 10 years in most jurisdictions

**CMA Code of Ethics**
Report any unprofessional conduct by colleagues to the appropriate authority

**CPSO Policy: Treating Self and Family Members**
Physicians will not diagnose or treat themselves or family members except for minor conditions or in emergencies and then only if no other physician is readily available

  - although the medical record is the property of the physician or an institution, the patient or the patient's delegate must be:
    - allowed full access to information in the medical record
    - patient or delegate must obtain access within a reasonable period of time
    - usually upon written request by the patient or patient's delegate
    - physician can charge a reasonable fee for this service
- in the hospital, physicians must ensure their own competence, respect hospital by-laws and regulations, practice only within the limits of granted privileges, cooperate with other hospital personnel, and maintain adequate hospital records

# Research Ethics

- involves the systematic analysis of ethical dilemmas arising during research involving human subjects to ensure that:
  - study participants are protected
  - clinical research is conducted to serve the interests of the participants and/or society as a whole
- major ethical dilemmas arise when a physician's obligation to the patient comes into conflict with other obligations and incentives
- any exceptions to disclosure for therapeutic consent do not apply in an experimental situation
- important ethical principles to consider when conducting research on human subjects are laid out in the *Declaration of Helsinki, the Belmont Report*, and the *Tri-Council Policy Statement: Ethical Conduct on Research Involving Human Subjects*

**Table 5. Ethical Principles for Research Involving Human Subjects**

| |
|---|
| Patient's participation in research should not put them at a known or probable disadvantage with respect to medical care (i.e. cannot deny participants in research 'known effective care', such as randomizing patients with depression to a placebo arm with no treatment) |
| Participant's voluntary and informed choice is usually required, except in special circumstances (i.e. chart reviews without patient contact, or emergency situations for which there is no accepted or helpful standard of care and the proposed intervention is not likely to cause more harm than such patients already face) |
| Access to the treatment that is considered standard (i.e. placebo-controlled trials are generally acceptable where patients still receive the standard of care, or, if not, are informed about the placebo arm and what that entails) |
| Must employ a scientifically valid design to answer the research question (ensured via peer review, expert opinion) |
| Must demonstrate sufficient value to justify any risk posed to participants |
| Must be conducted honestly (i.e. carried out as stated in the approved protocol) |
| Findings must be reported promptly and accurately without exaggeration, to allow practicing clinicians to draw reasonable conclusions |
| Patients must not be enticed into risky research by financial incentives and investigators must not trade the interests of patients for disproportionate recompense by a sponsor; both participants and investigators are due fair recompense for their time and efforts |
| Any significant interventional trial ought to have a data safety monitoring board that is independent of the sponsor and can ensure safety of the ongoing trial |

**Guiding Principles for Research Ethics**
- Respect for persons: informed consent
- Beneficence: harm vs. benefit
- Justice: avoid exploitation/unjustified exclusion

**Informed Consent for Research**
- Purpose of study
- Sum of funding
- Name and probability of harm and benefits
- Nature of physician's participation including compensation
- Proposals for research must be submitted to a research ethics board

Randomization is allowed even if there is an efficacious standard if, for example, there are drawbacks to it (such as it doesn't work for all, has side effects, and is not tolerated). In such cases, there must be a good safety net established to make sure subjects in the placebo arm do not deteriorate (i.e. there must be a safety monitoring plan for such studies)

**CMA and CPSO Guidelines for Ethically Appropriate Physician-Industry Relations**
- The primary goal should be the advancement of the health of Canadians
- Relationships should be guided by the CMA Code of Ethics
- The physician's primary obligation is to the patient
- Physicians should avoid any self-interest in their prescribing and referral practices
- Physicians should always maintain professional autonomy, independence, and commitment to the scientific method

# Physician-Industry Relations

- health care delivery in Canada involves collaboration between physicians and the pharmaceutical and health supply industries in the areas of research, education, and clinical evaluation packages (i.e. product samples)
- however, unlike physicians, pharmaceutical and health supply industries do not have a fiduciary duty to patients and are profit-driven
  - for example, the dissemination of free product samples by pharmaceutical companies is associated with increased patient preference for new drugs that are often more expensive, thus incurring a greater long-term cost for patients and the healthcare system
  - new pharmaceutical products are not always more effective than previous standard of care and may have less robust safety evidence by virtue of being new drugs
- physicians must ensure that their participation in such collaborative efforts is in keeping with their duties to their patients and society; however, physicians often struggle to properly identify situations in which a conflict of interest is present
- even seemingly innocuous gifts or other interactions (pens with pharmaceutical logo, research honoraria, meals, speaker fees, etc.) can subconsciously influence physician practices and beliefs in favour of promoted products, resulting in the prescription of medications for reasons other than their efficacy and safety profile
- gifts or free products from the pharmaceutical industry are usually inappropriate:
  - sponsorship for travel and fees for conference attendance may be accepted only where the physician is a conference presenter and not just in attendance
  - physicians receiving such sponsorship must disclose this at presentations and/or in written articles

# Resource Allocation

- **definition**: the distribution of goods and services to programs and people
- physicians have the duty to inform patients about therapeutic options even if they are not available
- physicians must make health care resources available to patients in a manner which is fair and equitable, without bias or discrimination
  - need and benefit are morally relevant criteria for resource allocation
  - gender, sexual orientation, religion, level of education, or age **alone** are morally irrelevant criteria. Must be weighed against need and benefit to justify equitable allocation of resources
- ethical dilemmas that arise when deciding how best to allocate resources
  - fair chances vs. best outcome: favouring best outcome vs. giving all patients fair access to limited resources (e.g. transplant list prioritization)
  - priorities problem: how much priority should the sickest patients receive?
  - aggregation problem: modest benefits to many vs. significant benefits to few
  - democracy problem: when to rely on a fair democratic process to arrive at a decision

### Guidelines for Appropriately Allocating Resources

- the physician's primary obligation is to:
  - protect and promote the welfare and best interests of their patients
  - choose interventions known to be beneficial on the basis of evidence of effectiveness
  - seek the tests or treatments that will accomplish the diagnostic or therapeutic goal for the least cost
  - advocate for one's patients, but avoid manipulating the system to gain unfair advantage for them
  - resolve conflicting claims for scarce resources justly, on the basis of morally relevant criteria such as need and benefit, using fair and publicly defensible procedures
  - inform patients of the impact of cost constraints on care, but in a sensitive way
  - seek resolution of unacceptable shortages at the level of hospital management or government

# Conscientious Objection

### Patients Refusing Treatment

- in accordance with the principle of autonomy, it is generally acceptable for competent patients to refuse medical interventions for themselves or others, although exceptions may occur
- the onus of justifying reasons for refusal or agreement is higher on SDMs than on capable patients
- if parents or SDMs make decisions that are clearly not in the "best interests" of an incapable child, physicians may have ethical grounds for administering treatment, depending on the acuity of the clinical situation
  - in high-acuity scenarios (e.g. refusing blood transfusion based on religious grounds for a child in hemorrhagic shock), physicians have a stronger obligation to act in the child's best interests
  - in lower acuity scenarios (e.g. refusing childhood immunization in a developed nation) there is a stronger obligation to respect the autonomy of the decision-makers
  - in 2014, a child was found not to be "a child in need of protection" when her mother refused chemotherapy and pursued traditional Indigenous healing. While this decision purported to establish a new constitutional right to Indigenous healing, the decision was amended such that "the best interests of the child are paramount." These statements could be interpreted in contradiction with each other, so it is unclear what the current status of the law is. See *Hamilton Health Sciences Centre v. DH* for more information

### Physicians Refusing to Provide Treatment

- physicians may refuse to provide treatment or discontinue relationships with patients, but must ensure these patients can access services elsewhere by way of referring the patient to a willing practitioner (e.g. a pediatrician who refuses to treat an unvaccinated child should refer the family to another practice)



**Recommendations for Working with Families Who Refuse Childhood Immunization**
Pediatrics 2011;128:S167-174

1. Provide clear information about the risks and benefits of immunization and the diseases targeted.
2. Inform parents when their beliefs are unsupported by evidence.
3. Physicians can discontinue professional services but must comply with legal and ethical requirements. Parents are entitled to refuse treatment that a physician recommends; not every disagreement should result in discharge from practice.
4. Vaccine education for Complementary and Alternative Medicine providers.
5. Public education campaigns regarding immunization.
6. No-fault compensation for vaccine-related injury.

# Indigenous Legal and Health Policy

- Indigenous peoples collectively refers to original inhabitants of Canada and their descendants: First Nations, Inuit, and Métis peoples defined in the *Canadian Constitution Act*, 1982
  - First Nations traditional territory encompasses all of geographic Canada and constitutes many distinct communities and languages
  - Inuit refers to original inhabitants of arctic regions including Labrador, northern Quebec, Nunavut, and Northwest Territories
  - Métis are Indigenous people of both First Nations and European heritage
  - Canada's *Indian Act*, 1876, defined who is considered a "status Indian" and thus eligible for programs and services by federal and provincial agencies. Non-Status First Nations, are Indigenous people who are not a "Registered Indian" with the federal government
    - while used by the federal government and for legal proceedings, the terms "status/non-status Indian" are paternalistic and offensive
  - the *Daniels Decision*, 2016, the Federal Court of Canada, deemed Métis and non-status First Nations peoples be considered "Indians" under *Canadian Constitution Act* but no reparations in fiduciary duty or duty to consult have been made
- Indigenous Health Policy in Canada is made up of a complicated "patchwork" of policies, legislation and agreements between federal, provincial, municipal, and Indigenous governments which is in a constant state of flux; reviewed by the National Collaborating Centre for Indigenous Health (NCCIH): http://www.nccah-ccnsa.ca/en/publications.aspx?sortcode=2.8.10&publication=28
  - while some Indigenous health services are adequate, gaps and ambiguities created by complicated policy and jurisdictions have created barriers to health equity
  - for on-reserve First Nations and Inuit, the federal government finances and administers health services through the First Nations and Inuit Health Branch (FNIHB)
  - the *Indian Health Policy*, 1979, and *Health Transfer Policy*, 1989, transferred control to individual communities to negotiate with the FNIHB varying levels of health care responsibility to the community or council level
  - treaties and Self Government Agreements can define areas of jurisdiction for federal, provincial/territorial, and First Nations governments

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# A Anesthesia and Perioperative Medicine

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# Acronyms

| | |
|---|---|
| 2,3-BPG | 2,3-Bisphosphoglycerate |
| ABG | arterial blood gas |
| ACC | American College of Cardiology |
| ACh | acetylcholine |
| AChE | acetylcholinesterase |
| ACV | assist-control ventilation |
| AHA | American Heart Association |
| ALS | amyotrophic lateral sclerosis |
| ARDS | acute respiratory distress syndrome |
| atm | atmosphere |
| CCS | Canadian Cardiovascular Society |
| CHF | congestive heart failure |
| CK | creatine kinase |
| CO | cardiac output |
| CSF | cerebrospinal fluid |
| CVP | central venous pressure |
| DIC | disseminated intravascular coagulation |
| DKA | diabetic ketoacidosis |
| $ETCO_2$ | End-Tidal $CO_2$ |
| ETT | endotracheal tube |
| $FiO_2$ | fraction of oxygen in inspired air |
| FFP | fresh frozen plasma |
| FRC | functional residual capacity |
| GA | general anesthesia |
| GERD | gastroesophageal reflux disease |
| Hb(i) | initial hemoglobin |
| Hb(f) | final hemoglobin |
| Hct | hematocrit |
| HES | hydroxyethyl starch |
| HHS | hyperosmolar hyperglycemic state |
| ICP | intracranial pressure |
| ICS | inhaled corticosteroids |
| IOP | intraocular pressure |
| ITP | immune thrombocytopenic purpura |
| LA | local anesthetic |
| LABA | long-acting β-agonist |
| LES | lower esophageal sphincter |
| LMA | laryngeal mask airway |
| LOC | level of consciousness |
| MAC | minimum alveolar concentration |
| MAP | mean arterial pressure |
| MH | malignant hyperthermia |
| MS | multiple sclerosis |
| NMJ | neuromuscular junction |
| NYHA | New York Heart Association |
| OCS | oral corticosteroids |
| OR | operating room |
| OSA | obstructive sleep apnea |
| $PaCO_2$ | arterial partial pressure of carbon dioxide |
| $PaO_2$ | arterial partial pressure of oxygen |
| PC | patient-controlled |
| PCA | patient-controlled analgesia |
| PCV | pressure-controlled ventilation |
| PEEP | positive end-expiratory pressure |
| PNS | parasympathetic nervous system |
| PONV | post-operative nausea and vomiting |
| PPV | positive pressure ventilation |
| RSI | rapid sequence induction |
| SABA | short-acting β-agonist |
| SCh | succinylcholine |
| SIADH | syndrome of inappropriate antidiuretic hormone |
| SNS | sympathetic nervous system |
| SV | stroke volume |
| SVR | systemic vascular resistance |
| TIA | transient ischemic attack |
| TBW | total body water |
| TIVA | total intravenous anesthetic |
| TURP | transurethral resection of prostate |
| V/Q | ventilation/perfusion |
| VT | ventricular tachycardia |
| VTE | venous thromboembolism |

# Overview of Anesthesia

- anesthesia: lack of sensation/perception

### Approach to Anesthesia

**Pre-operative**

1. pre-operative assessment
2. patient optimization

**Pre-operative/Peri-operative**

3. plan anesthetic
   various types of anesthesia
   pre-medication
   airway management
   monitors
   induction
   maintenance
   emergence
   tracheal extubation

**Post-operative**

4. post-operative care

# Types of Anesthesia

- **general**
  - general anesthesia (GA)
  - total IV anesthesia (TIVA)
- **regional**
  - spinal, epidural
  - peripheral nerve block
  - IV regional
- **local**
  - local infiltration
  - topical

Note that different types of anesthesia can be combined (general + regional)

# Pre-Operative Assessment



### Purpose

- identify concerns for medical and surgical management of patient
- allow for questions to help allay any fears or concerns patient and/or family may have
- arrange further investigations, consultations and treatments for patients not yet optimized
- plan and consent for anesthetic techniques

# History and Physical

### History

- age, gender
- indication for surgery
- surgical/anesthetic Hx: previous anesthetics, any complications, previous intubations, post-operative N/V
- FHx: abnormal anesthetic reactions, malignant hyperthermia, pseudocholinesterase deficiency (see *Uncommon Complications*, A28)
- medications, allergies (see *Pre-Operative Optimization: Medications*, A4)

- PMHx
  - neuro: seizures, TIA/strokes, raised ICP, spinal disease, aneurysm, conditions affecting neuromuscular junction (e.g. myasthenia gravis)
  - CVS: angina/CAD, MI, CHF, HTN, valvular disease, dysrhythmias, peripheral vascular disease (PVD), conditions requiring endocarditis prophylaxis, exercise tolerance, CCS/NYHA class (see Cardiology and Cardiac Surgery, C26, C35 sidebar for New York Heart Association Classification)
  - respiratory: smoking, asthma, COPD, recent upper respiratory tract infection (URTI), sleep apnea
  - GI: GERD, liver disease, NPO status
  - renal: acute vs. chronic renal insufficiency, dialysis, chronic kidney disease
  - hematologic: anemia, coagulopathies, blood dyscrasias
  - MSK: arthritides (e.g. rheumatoid arthritis, scleroderma), cervical spine pathology (e.g. cervical tumours, cervical infections/abscesses, trauma to cervical spine, previous cervical spine surgery), cervical spine instability (e.g. Trisomy 21)
  - endocrine: DM, thyroid disorders, adrenal disorders
  - other: morbid obesity, pregnancy, ethanol/recreational drug use

## Physical Exam

- weight, height, BP, heart rate, respiratory rate, oxygen saturation
- focused physical exam of the CNS, CVS, and respiratory systems
- general assessment of nutrition, hydration, and mental status
- airway assessment is done to determine intubation difficulty (no single test is specific or sensitive) and ventilation difficulty
  - cervical spine stability and neck movement – upper cervical spine extension, lower cervical spine flexion ("sniffing the morning air" position – Figure 6, Panel C)
  - Mallampati classification
  - "3-3-2 rule"
    - 3 of patient's own fingers can be placed between the incisors (incisor distance)
    - 3 fingers along the floor of the mandible between the mentum and hyoid bone (hyoid-mental distance)
    - 2 fingers in the superior laryngeal notch (thyroid-mouth distance)
    - thyromental distance (distance of lower mandible in midline from the mentum to the thyroid notch); <3 finger breadths (<6 cm) is associated with difficult intubation
    - mouth opening (<2 finger breadths is associated with difficult intubation)
    - anterior jaw subluxation (<1 finger breadth is associated with difficult intubation)
- tongue size
- dentition, dental appliances/prosthetic caps, existing chipped/loose teeth – pose aspiration risk if dislodged and must inform patients of rare possibility of damage
  - nasal passage patency (if planning nasotracheal intubation)
  - assess potential for difficult ventilation
- examination of anatomical sites relevant to lines and blocks
  - bony landmarks and suitability of anatomy for regional anesthesia (if relevant)
  - sites for IV, CVP, and pulmonary artery (PA) catheters

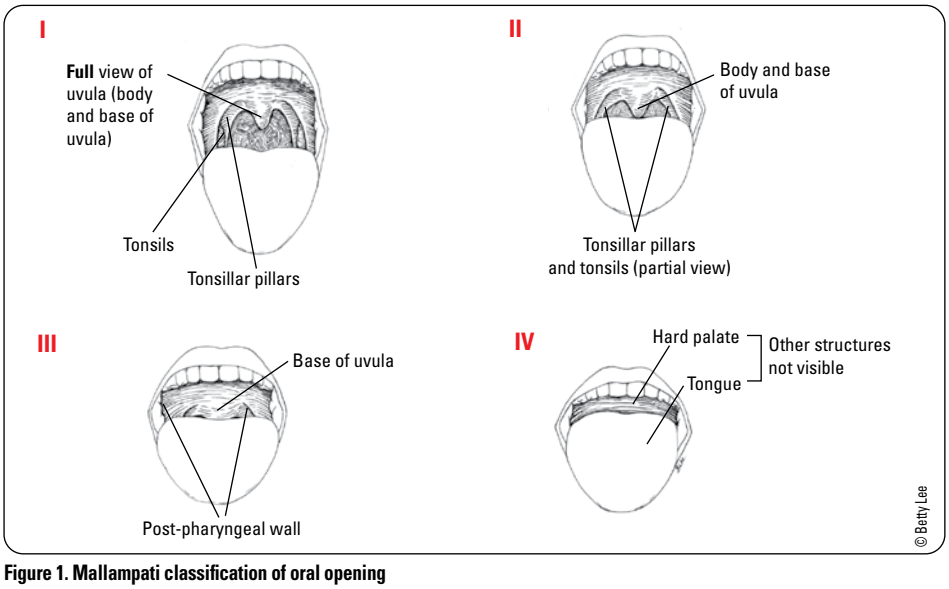



**Figure 1. Mallampati classification of oral opening**

**Evaluation of Difficult Airway**

**LEMON**
**L**ook – obesity, beard, dental/facial abnormalities, neck, facial/neck trauma
**E**valuate – 3-3-2 rule
**M**allampati score (≥3)
**O**bstruction – stridor, foreign bodies, masses
**N**eck mobility

**To Assess for Ventilation Difficulty**
Anesthesiology 2000,92:1229-36

**BONES**
**B**eard
**O**besity (BMI>26)
**N**o teeth
**E**lderly (age>55)
**S**noring Hx (sleep apnea)




**Figure 2. 3-3-2 Rule**

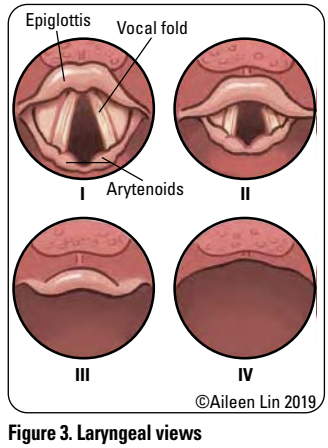



**Figure 3. Laryngeal views**

# Pre-Operative Investigations

- routine pre-operative investigations are only necessary if there are comorbidities or certain indications

**Table 1. Suggested Indications for Specific Investigations in the Pre-Operative Period**

| Test | Indications |
|---|---|
| **CBC** | Major surgery requiring group and screen or cross and match; chronic cardiovascular, pulmonary, renal, or hepatic disease; malignancy; known or suspected anemia; bleeding diathesis or myelosuppression; patient <1 yr of age |
| **Sickle Cell Screen** | Genetically predisposed patient (hemoglobin electrophoresis if screen is positive) |
| **INR, aPTT** | Anticoagulant therapy, bleeding diathesis, liver disease |
| **Electrolytes and Creatinine** | Hypertension, renal disease, DM, pituitary or adrenal disease; vascular disease, digoxin, diuretic, or other drug therapies affecting electrolytes |
| **Fasting Glucose Level** | DM (repeat on day of surgery) |
| **Pregnancy (β-hCG)** | Women of reproductive age |
| **ECG** | Heart disease, DM, other risk factors for cardiac disease; subarachnoid or intracranial hemorrhage, cerebrovascular accident, head trauma |
| **Chest Radiograph** | Patients with new or worsening respiratory symptoms/signs |

Guidelines to the Practice of Anesthesia Revised Edition 2013. Supplement to the Canadian Journal of Anesthesia, Vol 60, Dec. 2013. Reproduced with permission © Canadian Anesthesiologists' Society

# American Society of Anesthesiology Classification

- common classification of physical status at the time of surgery
- a gross predictor of overall outcome, NOT used as stratification for anesthetic risk (mortality rates)
- **ASA 1**: a healthy, fit patient
- **ASA 2**: a patient with mild systemic disease
  - e.g. controlled Type 2 DM, controlled essential HTN, obesity, smoker
- **ASA 3**: a patient with severe systemic disease that limits activity
  - e.g. stable CAD, COPD, DM, obesity
- **ASA 4**: a patient with incapacitating disease that is a constant threat to life
  - e.g. unstable CAD, renal failure, acute respiratory failure
- **ASA 5**: a moribund patient not expected to survive 24 h without surgery
  - e.g. ruptured abdominal aortic aneurysm (AAA), head trauma with increased ICP
- **ASA 6**: declared brain dead, a patient whose organs are being removed for donation purposes
- for emergency operations, add the letter E after classification (e.g. ASA 3E)

# Pre-Operative Optimization

- in general, prior to elective surgery:
  - any fluid and/or electrolyte imbalance should be corrected
  - extent of existing comorbidities should be understood, and these conditions should be optimized prior to surgery
  - medications may need adjustment

# Medications

- pay particular attention to cardiac and respiratory medications, opioids and drugs with many side effects and interactions
- **pre-operative medications to consider**
  - prophylaxis
    - risk of GE reflux: sodium citrate and/or ranitidine and/or metoclopramide 30 min-1 h prior to surgery
    - risk of infective endocarditis, GI/GU interventions: antibiotics
    - risk of adrenal suppression: steroid coverage
    - anxiety: consider benzodiazepines
    - COPD, asthma: bronchodilators
    - CAD risk factors: nitroglycerin and β-blockers
- **pre-operative medications to stop**
  - oral antihyperglycemics: do not take on morning of surgery
  - ACEI and angiotensin receptor blockers: do not take on the day of surgery (controversial – they increase the risk of hypotension post-induction but have not been shown to increase mortality or adverse outcomes; therefore, some people hold and some do not)
  - warfarin (consider bridging with heparin), anti-platelet agents (e.g. clopidogrel), Xa inhibitor, direct thrombin inhibitors

**Will This Patient Be Difficult to Intubate?**
JAMA 2019;321:493-503
**Objective**: To identify risk factors and physical findings that predict difficult intubation.
**Methods**: Systematic review of MEDLINE and EMBASE databases.
**Results**: 62 studies, 33,559 patients. Physical examination findings that best predicted a difficult intubation included grade of class 3 on upper lid bite test (lower incisors cannot reach upper lip; LR 14, 95% CI 9.9-22), shorter hyomental distance (<3-5.5 cm; LR 9.4, 95% 4.1-10), retrognathia (mandible <9 cm from angle of jaw to tip of chin; LR 6.0, 95% CI 3.1-11), and a Mallampati score ≥3 (LR 4.1, 95% CI 3.0-5.6).

**Impact of Anesthesia Management Characteristics on Severe Morbidity and Mortality**
Anesth 2005;102:257-268
**Study**: Case-control study of patients undergoing anesthesia.
**Patients**: 807 cases and 883 controls were analyzed among a cohort of 869,483 patients undergoing anesthesia between 1995-1997. Cases were defined as patients who either remained comatose or died within 24 h of receiving anesthesia. Controls were defined as patients who neither remained comatose nor died within 24 h of receiving anesthesia.
**Intervention**: General, regional, or combined anesthesia to patients undergoing a surgical procedure.
**Main Outcome**: Coma or death within 24 h of receiving anesthesia.
**Results**: The incidence of 24 h post-operative death was 8.8 per 10,000 anesthetics (95% CI 8.2-9.5) and the incidence of coma was 0.5 (95% CI 0.3-0.6). Anesthesia management risk factors that were associated with a decreased risk of morbidity and mortality were equipment check with protocol and documentation, directly available anesthesiologist with no change during anesthesia, 2 persons present at emergence of anesthesia, reversal of muscle relaxation, and post-operative pain medication.

**Continuation versus Discontinuation of Antiplatelet Therapy for Bleeding and Ischaemic Events in Adults Undergoing Non-Cardiac Surgery**
Cochrane DB Syst Rev 2018; CD012584
**Objective**: To compare continuation vs. discontinuation of antiplatelet therapy on the occurrence of bleeding and ischaemic events in adults undergoing non-cardiac surgery.
**Methods**: RCTs in Cochrane Central Register of Controlled Trials, MEDLINE, and Embase that compared adults taking single or dual antiplatelet therapy for at least two weeks, including patients with at least one cardiac risk factor. Included general, spinal, and regional anesthesia and excluded minor procedures involving only local anesthetic/sedation.
**Results**: 5 trials, 666 adult patients. Continuation or discontinuation had no difference on mortality at 30 d post-op (RR 1.21, 95% CI 0.34-4.27), blood loss (RR 1.37, 95% CI 0.83-2.26), or ischaemic events within 30 d of surgery (RR 0.67, 95% CI 0.25-1.77).
**Conclusions**: Moderate evidence supporting continuation or discontinuation of antiplatelet therapy makes no difference on bleeding requiring transfusion. Low evidence supporting no difference in mortality or ischaemic events.

- discuss perioperative use of ASA, NSAIDs with surgeon (± patient's cardiologist/internist)
- in patients undergoing non-cardiac surgery, starting or continuing low-dose ASA in the perioperative period does not appear to protect against post-operative MI or death, but increases the risk of major bleeding
  - note: this does not apply to patients with bare metal stents or drug-eluting coronary stents
- herbal supplements: stop one week prior to elective surgery (ephedra, garlic, ginko, ginseng, kava, St. John's Wort, Valerian, Echinacea)

- **pre-operative medications to adjust**
  - insulin (consider insulin/dextrose infusion or holding dose), prednisone, bronchodilators



**Perioperative β-blockers for Preventing Surgery-related Mortality and Morbidity**
Cochrane DB Syst Rev 2018; CD004476
**Objectives**: Effects of perioperative β-blockers for prevention of surgery-related mortality and morbidity in patients undergoing any type of surgery while under general anesthesia.
**Outcomes**:
Cardiac surgery: Perioperative β-blockers associated with reduced supraventricular (RR 0.44, 95% CI 0.36-0.53) and ventricular (RR 0.37, 95% CI 0.24-0.58) arrhythmias in the aftermath of surgery. Effect on mortality, AMI, stroke, CHF, hypotension, and bradycardia unclear.
Non-cardiac surgery: Perioperative β-blockers associated with decreased incidence of supraventricular arrhythmias (RR 0.73, 95% CI 0.57-0.94) and AMI (RR 0.73, 95% CI 0.61-0.87). However, this is potentially offset by increased all-cause mortality (RR 1.25, CI 95% 1.00-1.57) with potential increase in stroke rate (RR 1.59, 95% CI 0.93-2.71).

## Hypertension

- BP <180/110 is not an independent risk factor for perioperative cardiovascular complications
- target sBP <180 mmHg, dBP <110 mmHg
- assess for end-organ damage and treat accordingly

## Coronary Artery Disease

- ACC/AHA Guidelines (2014) recommend that at least 60 d should elapse after a MI before a non-cardiac surgery in the absence of a coronary intervention
  - this period carries an increased risk of re-infarction/death
  - if operative procedure is essential and cannot be delayed then invasive intra- and post-operative ICU monitoring is required to reduce the above risk
- mortality with perioperative MI is 20-50%
- perioperative β-blockers
  - may decrease cardiac events and mortality (but increases risk of perioperative strokes)
  - continue β-blocker if patient is routinely taking it prior to surgery
  - consider initiation of β-blocker in:
    - patients with CAD or indication for β-blocker
    - intermediate or high risk surgery, especially vascular surgery

## Respiratory Diseases

- smoking
  - adverse effects: altered mucus secretion and clearance, decreased small airway calibre, altered oxygen carrying capacity, increased airway reactivity, and altered immune response
  - abstain at least 8 wk pre-operatively if possible
  - if unable, abstaining even 24 h pre-operatively has been shown to increase oxygen availability to tissues
- asthma
  - pre-operative management depends on degree of baseline asthma control
  - increased risk of bronchospasm from intubation
  - administration of short course (up to 1 wk) pre-operative corticosteroids and inhaled β2-agonists decreases the risk of bronchospasm and does not increase the risk of infection or delay wound healing
  - avoid non-selective β-blockers due to risk of bronchospasm (cardioselective β-blockers (metoprolol, atenolol) do not increase risk in the short-term)
  - delay elective surgery for poorly controlled asthma (increased cough or sputum production, active wheezing)
  - ideally, delay elective surgery by a minimum of 6 wk if patient develops URTI
- COPD
  - anesthesia, surgery (especially abdominal surgery, in particular upper abdominal surgery) and pain predispose the patient to atelectasis, bronchospasm, pneumonia, prolonged need for mechanical ventilation, and respiratory failure
  - pre-operative ABG is needed for all COPD stage II and III patients to assess baseline respiratory acidosis and plan post-operative management of hypercapnea
  - cancel/delay elective surgery for acute exacerbation



**β-blockers**
- β1-receptors are located primarily in the heart and kidneys
- β2-receptors are located in the smooth muscle (i.e. bronchi, uterus)
- Non-selective β-blockers block β1 and β2-receptors (labetalol*, carvedilol**, nadolol). Caution is required with non-selective β-blockers, particularly in patients with respiratory conditions where β2 blockade can result in airway reactivity

*labetalol is both an α- and β-blocker
**carvedilol is also both an alpha and beta blocker

## Aspiration

- increased risk of aspiration with:
  - decreased LOC (drugs/alcohol, head injury, CNS pathology, trauma/shock)
  - delayed gastric emptying (non-fasted within 8 h, diabetes, narcotics)
  - decreased sphincter competence (GERD, hiatus hernia, nasogastric tube, pregnancy, obesity)
  - increased abdominal pressure (pregnancy, obesity, bowel obstruction, acute abdomen)
  - unprotected airway (laryngeal mask vs. ETT)
- management
  - manage risk factors if possible
  - utilize protected airway (i.e. endotracheal tube)
  - reduce gastric volume and acidity
  - delay inhibiting airway reflexes with muscular relaxants
  - employ rapid sequence induction (see *Rapid Sequence Induction*, A15)

# Fasting Guidelines

### Fasting Guidelines Prior to Surgery (Canadian Anesthesiologists' Society)

- before elective procedures, the minimum duration of fasting should be:
  - **8 h** after a meal that includes meat, fried or fatty foods
  - **6 h** after a light meal (such as toast or crackers) or after ingestion of infant formula or non-human milk
  - **4 h** after ingestion of breast milk
  - **2 h** after clear fluids (water, black coffee, tea, carbonated beverages, juice without pulp)

# Hematological Disorders

- history of congenital or acquired conditions (sickle cell anemia, factor VIII deficiency, ITP, liver disease)
- evaluate hemoglobin, hematocrit and coagulation profiles when indicated (see Table 1)
- anemia
  - pre-operative treatments to increase hemoglobin (PO or IV iron supplementation, erythropoietin or pre-admission blood collection in certain populations)
- coagulopathies
  - discontinue or modify anticoagulation therapies (warfarin, clopidogrel, ASA, apixaban, dabigatran) in advance of elective surgeries
  - administration of reversal agents if necessary: vitamin K, FFP, prothrombin complex concentrate, recombinant activated factor VII

**Preoperative Anemia and Postoperative Outcomes in Non-Cardiac Surgery: a Retrospective Cohort Study**
Lancet 2011; 378: 1396-1407
**Objectives**: Assess effect of preoperative anaemia on 30 d postoperative morbidity and mortality in patients undergoing major non-cardiac surgery.
**Methods**: Patients undergoing major non-cardiac surgery in 2008 from the American College of Surgeons' National Surgical Quality Improvement Program database.
**Results**: 227 425 adult patients. Postoperative mortality at 30 d was higher in patients with anaemia than those without (OR 1.42, 95% CI 1.31-1.54).
**Outcomes**: Preoperative anaemia, even to a mild degree, is independently associated with an increased risk of 30 d morbidity and mortality.

# Endocrine Disorders

- Diabetes Mellitus (DM)
  - clarify type 1 vs. type 2
  - clarify treatment – oral anti-hyperglycemics and/or insulin
  - assess glucose control with history and HbA1c; well controlled diabetics have more stable glucose levels intraoperatively
  - end organ damage: be aware of damage to cardiovascular, renal, and central, peripheral and autonomic nervous systems
  - preoperative guidelines for DM:
    - 1. verify target blood glucose concentration with frequent glucose monitoring: <10 mmol/L in critical patients, <7.8 mmol/L in stable patients)
    - 2. use insulin therapy to maintain glycemic goals
    - 3. hold biguanides, **α**-glucosidase inhibitors, thiazolidinediones, sulfonylureas and GLP-1 agonists on the morning of surgery
    - 4. consider cancelling nonemergency procedures if patient presents with metabolic abnormalities (DKA, HHS, etc.) or glucose reading above 22.2-27.7 mmol/L
  - formulate intraoperative glucose management plan based on type (1 vs. 2), glucose control, and extent of end organ damage
- hyperthyroidism and hypothyroidism
  - hyperthyroidism: can experience sudden release of thyroid hormone (thyroid storm) if not treated or well-controlled pre-operatively; treatment: **β**-blockers and pre-operative prophylaxis
- adrenocortical insufficiency (Addison's, exogenous steroid use)
  - consider intraoperative steroid supplementation

# Obesity and Obstructive Sleep Apnea

- assess for co-morbid conditions in obese patient (independent risk factor for CVD, DM, OSA, cholelithiasis, HTN)
- previously undiagnosed conditions may require additional testing to characterize severity
- severity of OSA may be determined from sleep studies and level of pressure prescribed for home CPAP device
- both obesity and OSA independently increase risk of difficult ventilation, intubation and post-operative respiratory complications

# Monitoring

### Canadian Guidelines to the Practice of Anesthesia and Patient Monitoring

- an anesthetist present: "the only indispensable monitor"
- a completed pre-anesthetic checklist: including ASA class, NPO policy, Hx and investigations
- a perioperative anesthetic record: HR and BP every 5 min, $O_2$ saturation, End Tidal $CO_2$, dose and route of drugs and fluids
- continuous monitoring: see *Routine Monitors for All Cases*, A7

**Pre-Anesthetic Checklist**

**MS MAIDS**
**M**achine: connected, pressures okay, all metres functioning, vaporizers full
**S**uction: connected and working
**M**onitor: all monitors appropriate for the case
**A**irway: laryngoscope and blades, ETT, syringe, stylet, oral and nasal airways, tape, bag, and mask
**I**V: second IV set-up and ready if needed
**D**rugs: case-specific drugs ready and emergency medications in correct location and accessible
**S**pecial equipment: OG tube, CVP monitor, shoulder roll, etc.

### Routine Monitors for All Cases

- pulse oximeter, BP monitor, electrocardiography, capnography (required for general anesthesia and deep procedural sedation, Ramsey Sedation Scale 4-6), and an agent-specific anesthetic gas monitor when inhalational anesthetic agents are used
- the following must also be available: temperature probe, peripheral nerve stimulator, stethoscope, appropriate lighting, spirometry, manometer to measure endotracheal tube cuff pressure

### Elements to Monitor

- anesthetic depth
  - end-tidal inhaled anesthetic monitoring and EEG monitoring, such as a Bispectral Index monitor, can be used as assessments of anesthetic depth
  - inadequate: blink reflex present when eyelashes lightly touched, HTN, tachycardia, tearing or sweating. However, these findings are non-specific
  - excessive: hypotension, bradycardia
- oxygenation: pulse oximetry, $FiO_2$
- ventilation: verify correct position of ETT, chest excursions, breath sounds, $ETCO_2$ analysis, end tidal inhaled anesthesia analysis
- circulation: heart rate, rhythm, BP, telemetry, oximetry, pulmonary capillary wedge pressure
- temperature
- hourly urine output

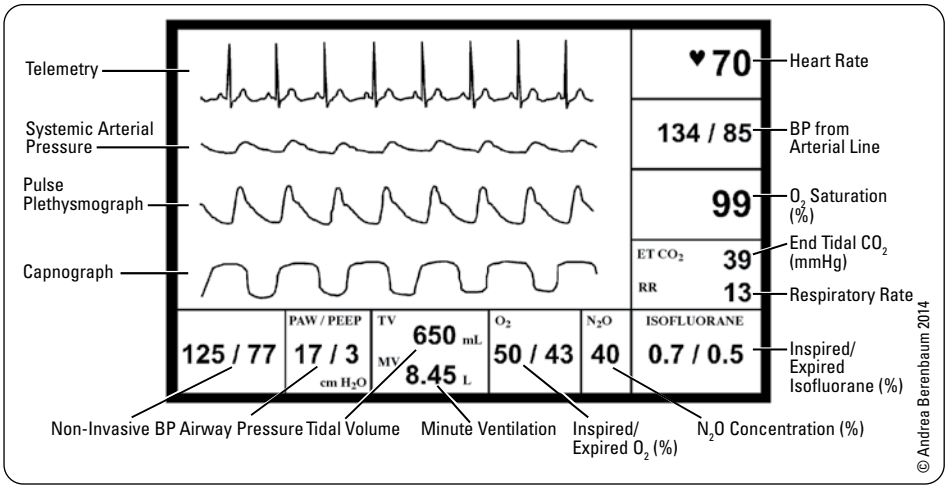



**Figure 4. Typical anesthesia monitor**

# Airway Management

## Airway Anatomy

- resistance to airflow through nasal passages accounts for approximately 2/3 of total airway resistance
- pharyngeal airway extends from posterior aspect of the nose to cricoid cartilage
- glottic opening (triangular space formed between the true vocal cords) is the narrowest segment of the laryngeal opening in adults
- the glottic opening is the space through which one visualizes proper placement of the ETT
- the trachea begins at the level of the thyroid cartilage, C6, and bifurcates into the right and left main bronchi at T4-T5 (approximately the sternal angle)

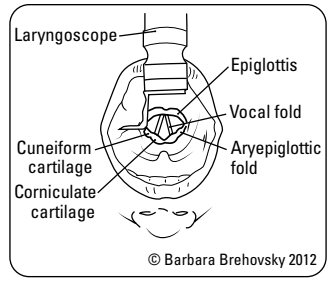



**Figure 5. Landmarks for intubation**

## Methods of Supporting Airways

1. non-definitive airway (patent airway)
   - jaw thrust/chin lift
   - oropharyngeal and nasopharyngeal airway
   - bag mask ventilation
   - LMA
2. definitive airway (patent and protected airway)
   - ETT
   - surgical airway (cricothyrotomy or tracheostomy)

**Table 2. Methods of Supporting the Airway**

| | Bag and Mask | Laryngeal Mask Airway (LMA) | Endotracheal Tube (ETT) |
|---|---|---|---|
| **Advantages/ Indications** | Basic<br>Non-invasive<br>Readily available | Easy to insert<br>Less airway trauma/irritation than ETT<br>Frees up hands (vs. face mask)<br>Primarily used in spontaneously ventilating patient | Indications for intubation (5 Ps)<br>**P**atent airway<br>**P**rotects against aspiration<br>**P**ositive pressure ventilation<br>**P**ulmonary toilet (suction)<br>**P**harmacologic administration during hemodynamic instability |
| **Disadvantages/ Contraindications** | Risk of aspiration if decreased LOC<br>Cannot ensure airway patency<br>Inability to deliver precise tidal volume<br>Operator fatigue | Risk of gastric aspiration<br>PPV<20 cm $H_20$ needed<br>Oropharyngeal/retropharyngeal pathology or foreign body<br>Does not protect against laryngospasm or gastric aspiration | Insertion can be difficult<br>Muscle relaxant usually needed<br>Most invasive – see *Complications During Laryngoscopy and Intubation*, A9 |
| **Other** | Facilitate airway patency with jaw thrust and chin lift<br>Can use oropharyngeal/ nasopharyngeal airway | Sizing by body weight (approx)<br>40-50 kg: 3<br>50-70 kg: 4<br>70-100 kg: 5 | Auscultate to avoid endobronchial intubation<br>Sizing (approx):<br>Male: 8.0-9.0 mm<br>Female: 7.0-8.0 mm<br>Pediatric Uncuffed (>age 2): (age/4) + 4 mm |

# Tracheal Intubation

## Preparing for Intubation

- failed attempts at intubation can make further attempts more difficult due to tissue trauma
- plan, prepare, and assess for potential difficulties (see *Pre-Operative Assessment*, A2)
- ensure equipment is available and working (test ETT cuff, check laryngoscope light and suction, machine check)
- pre-oxygenate/denitrogenate: patient breathes 100% $O_2$ for 3-5 min or for 4-8 vital capacity breaths
- may need to suction mouth and pharynx first

## Proper Positioning for Intubation

- align the three axes (mouth, pharynx, and larynx) to allow visualization from oral cavity to glottis
  - "sniffing position": flexion of lower C-spine (C5-C6), bow head forward, and extension of upper C-spine at atlanto-occipital joint (C1), nose in the air
  - contraindicated in known/suspected C-spine fracture/instability
  - poor/no view of glottic opening can be remediated by anterior lanryngeal pressure
- laryngoscope tip placed in the epiglottic vallecula in order to visualize cord

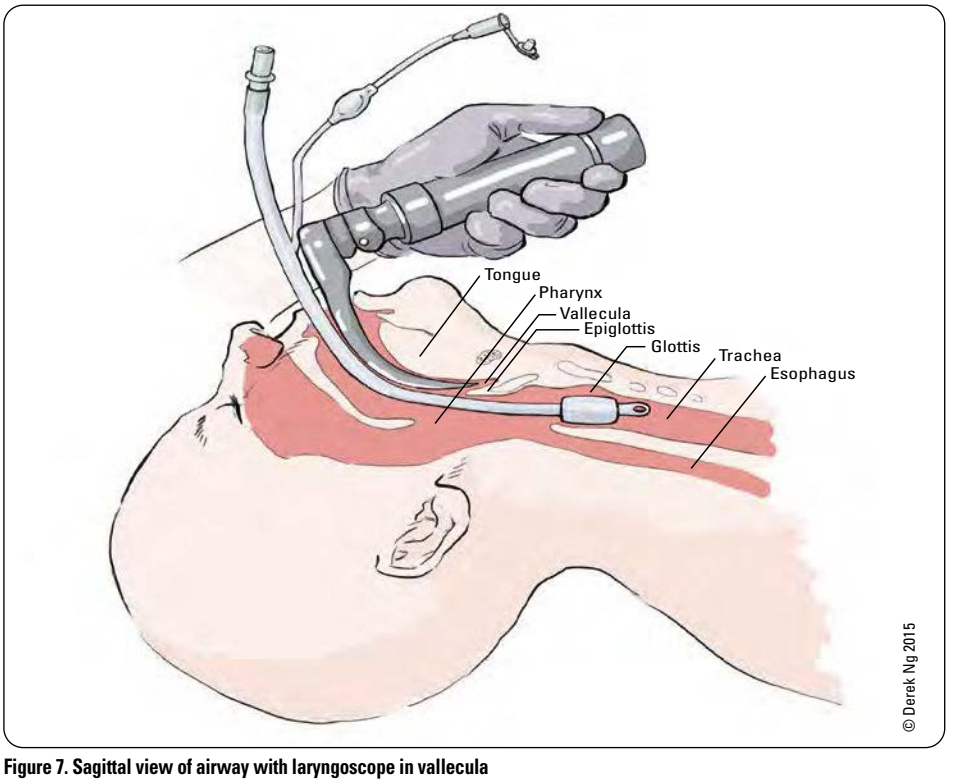



**Figure 7. Sagittal view of airway with laryngoscope in vallecula**

**Equipment for Intubation**

**MDSOLES**
**M**onitors
**D**rugs
**S**uction
**O**xygen source and self-inflating bag with oropharyngeal and nasopharyngeal airways
**L**aryngoscope
**E**ndotracheal tubes (appropriate size and one size smaller)
**S**tylet, **S**yringe for tube cuff inflation

**Medications that can be given through the ETT**

**NAVEL**
**N**aloxone
**A**tropine
**V**entolin
**E**pinephrine
**L**idocaine

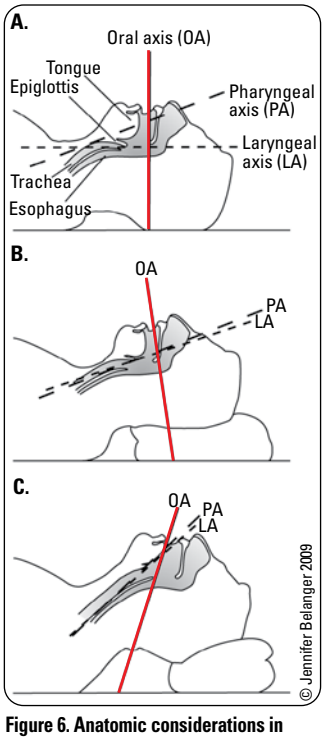



**Figure 6. Anatomic considerations in laryngoscopy**
A. Neutral position
B. C-spine flexion
C. C-spine flexion with atlanto-occipital extension

### Tube Insertion

- laryngoscopy and ETT insertion can incite a significant sympathetic response via stimulation of cranial nerves 9 and 10 due to a "foreign body reflex" in the trachea, including tachycardia, dysrhythmias, myocardial ischemia, increased BP, and coughing
- a malpositioned ETT is a potential hazard for the intubated patient
  - if too deep, may result in right endobronchial intubation, which is associated with left-sided atelectasis and right-sided tension pneumothorax
  - if too shallow, may lead to accidental extubation, vocal cord trauma, or laryngeal paralysis as a result of pressure injury by the ETT cuff
- the tip of ETT should be located at the midpoint of the trachea at least 2 cm above the carina and the proximal end of the cuff should be placed at least 2 cm below the vocal cords
- approximately 20-23 cm mark at the right corner of the mouth for men and 19-21 cm for women

**Differential Diagnosis of Poor Bilateral Breath Sounds after Intubation**

**DOPE**
**D**isplaced ETT
**O**bstruction
**P**neumothorax
**E**sophageal intubation

### Confirmation of Tracheal Placement of Endotracheal Tube

- direct
  - visualization of ETT passing through cords
  - bronchoscopic visualization of ETT in trachea
- indirect
  - $ETCO_2$ in exhaled gas measured by capnography – a mandatory method for confirming the ETT is in the airway
  - auscultate for equal breath sounds bilaterally and absent breath sounds over epigastrium
  - bilateral chest movement, condensation of water vapour in ETT visible during exhalation and no abdominal distention
  - refilling of reservoir bag during exhalation
  - CXR (rarely done): only confirms position of the tip of ETT and not whether the ETT is in the trachea
- esophageal intubation suspected when:
  - $ETCO_2$ zero or near zero on capnograph
  - abnormal sounds during assisted ventilation
  - impairment of chest excursion
  - hypoxia/cyanosis
  - presence of gastric contents in ETT
  - breath sounds heard when auscultating over epigastrium/LUQ
  - distention of stomach/epigastrium with ventilation

**Cormack-Lehane Classification of Laryngeal View (Figure 3)**

- Grade 1: all laryngeal structures revealed
- Grade 2: posterior laryngeal 2A (posterior vocal folds) 2B (arytenoids)
- Grade 3: Larynx concealed, only epiglottis
- Grade 4: Neither glottis nor epiglottis

### Complications During Laryngoscopy and Intubation

- dental damage
- laceration (lips, gums, tongue, pharynx, vallecula, esophagus)
- laryngeal trauma
- esophageal or endobronchial intubation
- accidental extubation
- insufficient cuff inflation or cuff laceration: results in leaking and aspiration
- laryngospasm (see *Extubation*, A20, for definition)
- bronchospasm

## Difficult Airway

- difficulties with bag-mask ventilation, supraglottic airway, laryngoscopy, passage of ETT through the cords, infraglottic airway or surgical airway
- algorithms exist for difficult airways (Can J Anesth 2013;60:1119-1138), see *Appendices*, A30
- pre-operative assessment (history of previous difficult airway, airway examination) and pre-oxygenation are important preventative measures
- if difficult airway expected, consider:
  - awake intubation
  - intubating with bronchoscope, trachlight (lighted stylet), fibre optic laryngoscope, glidescope, etc.
- if intubation unsuccessful after induction:
  1. CALL FOR HELP
  2. ventilate with 100% $O_2$ via bag and mask
  3. consider returning to spontaneous ventilation and/or waking patient
- if bag and mask ventilation inadequate:
  1. CALL FOR HELP
  2. attempt ventilation with oral airway
  3. consider/attempt LMA
  4. emergency invasive airway access (e.g. rigid bronchoscope, cricothyrotomy, or tracheostomy)

If you encounter difficulty with tracheal intubation, oxygenation is more important than intubation

# Oxygen Therapy

- in general, the goal of oxygen therapy is to maintain arterial oxygen saturation ($SaO_2$) at a minimum, >90%
- small decrease in saturation below $SaO_2$ of 90% corresponds to a large drop in $PaO_2$
- in intubated patients, oxygen is delivered via the ETT
- in patients not intubated, there are many oxygen delivery systems available; the choice depends on oxygen requirements ($FiO_2$) and the degree to which precise control of delivery is needed
- cyanosis can be detected at $SaO_2$ <85%, frank cyanosis at $SaO_2$ = 67%

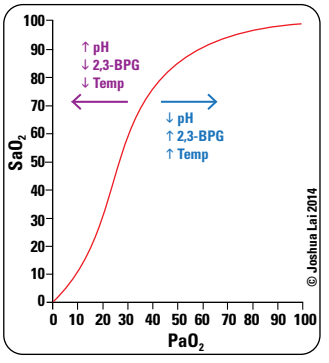


**Figure 8. $HbO_2$ saturation curve**

## Low Flow Systems

- provide $O_2$ at flows between 0-10 L/min
- acceptable if tidal volume 300-700 mL, respiratory rate (RR) <25, consistent ventilation pattern
- dilution of oxygen with room air results in a decrease in $FiO_2$
- an increase in minute ventilation (tidal volume x RR) results in a decrease in $FiO_2$
- e.g. nasal cannula (prongs)
  - well tolerated if flow rates <5-6 L/min; drying of nasal mucosa at higher flows
  - nasopharynx acts as an anatomic reservoir that collects $O_2$
  - delivered oxygen concentration ($FiO_2$) can be estimated by adding 4% for every additional litre of $O_2$ delivered
  - provides $FiO_2$ of 24-44% at $O_2$ flow rates of 1-6 L/min

## Reservoir Systems

- use a volume reservoir to accumulate oxygen during exhalation thus increasing the amount of oxygen available for the next breath
- simple face mask
  - covers patient's nose and mouth and provides an additional reservoir beyond nasopharynx
  - fed by small bore $O_2$ tubing at a rate of at least 6 L/min to ensure that exhaled $CO_2$ is flushed through the exhalation ports and not rebreathed
  - provides $FiO_2$ of 55% at $O_2$ flow rates of 10 L/min
- non-rebreather mask
  - a reservoir bag and a series of one-way valves prevent expired gases from re-entering the bag
  - during the exhalation phase, the bag accumulates with oxygen
  - provides $FiO_2$ of 80% at $O_2$ flow rates of 10-15 L/min

**Composition of Air**
78.1% nitrogen
20.9% oxygen
0.9% argon
0.04% carbon dioxide

## High Flow Systems

- generate flows of up to 50-60 L/min
- meet/exceed patient's inspiratory flow requirement
- deliver consistent and predictable concentration of $O_2$
- Venturi mask
  - delivers specific $FiO_2$ by varying the size of air entrapment
  - oxygen concentration determined by mask's port and NOT the wall flow rate
  - enables control of gas humidity
  - $FiO_2$ ranges from 24-50%

# Ventilation

- ventilation is maintained with PPV in patients given muscle relaxants
- assisted or controlled ventilation can also be used to assist spontaneous respirations in patients not given muscle relaxants as an artificial means of supporting ventilation and oxygenation

## Mechanical Ventilation

- indications for mechanical ventilation
  - apnea
  - hypoventilation/acute respiratory acidosis
  - intraoperative positioning limiting respiratory excursion (e.g. prone, Trendelenburg)
  - required hyperventilation (to lower ICP)
  - deliver positive end expiratory pressure (PEEP)
  - increased intrathoracic pressure (e.g. laparoscopic procedure)
- complications of mechanical ventilation
  - airway complications
    - tracheal stenosis, laryngeal edema
    - alveolar complications
    - ventilator-induced lung injury (barotrauma, volutrauma, atelectatrauma), ventilator-associated pneumonia (nosocomial pneumonia), inflammation, auto-PEEP, patient-ventilator asynchrony
    - cardiovascular complications
    - reduced venous return (secondary to increased intrathoracic pressure), reduced cardiac output, hypotension

Changes in peak pressures in ACV and tidal volumes in PCV may reflect changes in lung compliance and/or airway resistance – patient may be getting better or worse

**Positive End Expiratory Pressure (PEEP)**
- Positive pressure applied at the end of ventilation that helps to keep alveoli open, decreasing V/Q mismatch
- Used with all invasive modes of ventilation

**Tracheostomy**
- Tracheostomy should be considered in patients who require ventilator support for extended periods of time
- Shown to improve patient comfort and give patients a better ability to participate in rehabilitation activities

- neuromuscular complications
  - muscle atrophy
  - increased intracranial pressure
- metabolic
  - decreased $CO_2$ due to hyperventilation
  - alkalemia with over correction of chronic hypercarbia

## Ventilator Strategies

- mode and settings are determined based on patient factors (e.g. ideal body weight, compliance, resistance) and underlying reason for mechanical ventilation
- hypoxemic respiratory failure: ventilator provides supplemental oxygen, recruits atelectatic lung segments, helps improve V/Q mismatch, and decreases intrapulmonary shunt
- hypercapnic respiratory failure: ventilator augments alveolar ventilation; may decrease the work of breathing, allowing respiratory muscles to rest

## Modes of Ventilation

- assist-control ventilation (ACV) or volume control (VC)
  - every breath is delivered with a pre-set tidal volume and rate or minute ventilation
  - extra controlled breaths may be triggered by patient effort; if no effort is detected within a specified amount of time the ventilator will initiate the breath
- pressure control ventilation (PCV)
  - a minimum frequency is set and patient may trigger additional breaths above the ventilator
  - all breaths delivered at a preset constant inspiratory pressure
  - in traditional PCV, tidal volume is not guaranteed thus changes in compliance and resistance affect tidal volume
- synchronous intermittent mandatory ventilation (SIMV)
  - ventilator provides controlled breaths (either at a set volume or pressure depending on whether in VC or PCV, respectively)
  - patient can breathe spontaneously (these breaths may be pressure supported) between controlled breaths
- pressure support ventilation (PSV)
  - patient initiates all breaths and the ventilator supports each breath with a pre-set inspiratory pressure
  - useful for weaning off ventilator
- high-frequency oscillatory ventilation (HFOV)
  - high breathing rate (up to 900 breaths/min in an adult), very low tidal volumes
  - used commonly in neonatal and pediatric respiratory failure
  - occasionally used in adults when conventional mechanical ventilation is failing
- non-invasive positive pressure ventilation (NPPV)
  - achieved without intubation by using a nasal or face mask
  - BiPAP: increased pressure (like PSV) on inspiration and lower constant pressure on expiration (i.e. PEEP)
  - CPAP: delivers constant pressure on both inspiration and expiration

**Table 3. Causes of Abnormal End Tidal $CO_2$ Levels**

| Hypocapnea (Decreased $CO_2$) | Hypercapnea (Increased $CO_2$) |
|---|---|
| Hyperventilation | Hypoventilation |
| Hypothermia (decreased metabolic rate) | Hyperthermia and other hypermetabolic states |
| Decreased pulmonary blood flow (decreased cardiac output) | Improved pulmonary blood flow after resuscitation or hypotension |
| Technical issues<br>Incorrect placement of sampling catheter<br>Inadequate sampling volume | Technical issues<br>Water in capnography device<br>Anesthetic breathing circuit error<br>Inadequate fresh gas flow<br>Rebreathing<br>Exhausted soda lime<br>Faulty circuit absorber valves |
| V/Q mismatch<br>Pulmonary thromboembolism<br>Incipient pulmonary edema<br>Air embolism | Low bicarbonate |

**Monitoring Ventilatory Therapy**
- Pulse oximetry, end-tidal $CO_2$ concentration
- Regular arterial blood gases
- Assess tolerance regularly

Patients who develop a pneumothorax while on mechanical ventilation require a chest tube

**Causes of Intraoperative Hypoxemia**
**Inadequate Oxygen Supply**
e.g. breathing system disconnection, obstructed or malpositioned ETT, leaks in the anesthetic machine, loss of oxygen supply
**Hypoventilation**
**Ventilation-Perfusion Inequalities**
e.g. atelectasis, pneumonia, pulmonary edema, pneumothorax
**Reduction in Oxygen Carrying Capacity**
e.g. anemia, carbon monoxide poisoning, methemoglobinemia, hemoglobinopathy
**Leftward Shift of the Hemoglobin-Oxygen Saturation Curve**
e.g. hypothermia, decreased 2,3-BPG, alkalosis, hypocarbia, carbon monoxide poisoning
**Right-to-Left Cardiac Shunt**

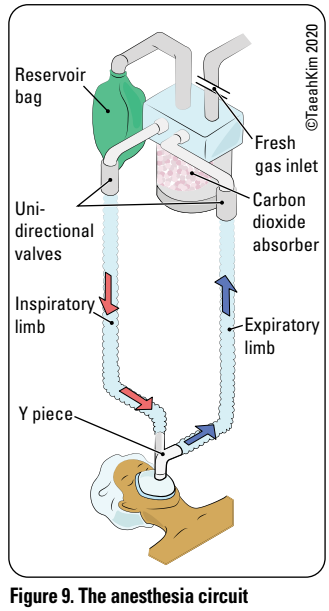



**Figure 9. The anesthesia circuit**

# Intraoperative Management

## Temperature

### Causes of Hypothermia (<36.0° C)

- intraoperative temperature losses are common (e.g. 90% of intraoperative heat loss is transcutaneous), due to:
  - OR environment (cold room, IV fluids, instruments)
  - open wound
- prevent with forced air warming blanket and warmed IV fluids

### Causes of Hyperthermia (>37.5-38.3° C)

- drugs (e.g. atropine)
- blood transfusion reaction
- infection/sepsis
- medical disorder (e.g. thyrotoxicosis)
- malignant hyperthermia (see *Uncommon Complications*, A28)
- over-zealous warming efforts

**Impact of Hypothermia (<36°C)**

- Increased risk of wound infections due to impaired immune function
- Increases the period of hospitalization by delaying healing
- Reduces platelet function and impairs activation of coagulation cascade increasing blood loss and transfusion requirements
- Triples the incidence of VT and morbid cardiac events
- Decreases the metabolism of anesthetic agents prolonging post-operative recovery

## Heart Rate

### Cardiac Arrest

- pulseless arrest occurs due to 4 cardiac rhythms divided into shockable and non-shockable rhythms
  - shockable: ventricular fibrillation (VF) and ventricular tachycardia (VT)
  - non-shockable: asystole and pulseless electrical activity (PEA)
- for VF/VT, key to survival is good early CPR and defibrillation
- for asystole/PEA, key to survival is good early CPR and exclusion of all reversible causes
- reversible causes of PEA arrest (5 Hs and 5 Ts)
  - 5 Hs: **h**ypothermia, **h**ypovolemia, **h**ypoxia, **h**ydrogen ions (acidosis), **h**ypo/**h**yperkalemia
  - 5 Ts: **t**amponade (cardiac), **t**hrombosis (pulmonary), **t**hrombosis (coronary), **t**ension pneumothorax, **t**oxins (overdose/poisoning)
  - when a patient sustains a cardiac arrest during anesthesia, it is important to remember that there are other causes on top the Hs and Ts to consider (i.e. local anesthetic systemic toxicity (LAST), excessive anesthetic dosing and others)
- for management of cardiac arrest, see *Appendices*, A32

### Intraoperative Tachycardia

- tachycardia = HR >150 bpm; divided into narrow complex supraventricular tachycardias (SVT) or wide complex tachycardias
- SVT: sinus tachycardia, atrial fibrillation/flutter, accessory pathway mediated tachycardia, paroxysmal atrial tachycardia
- wide complex tachycardia: VT, SVT with aberrant conduction
- causes of sinus tachycardia
  - shock/hypovolemia/blood loss
  - anxiety/pain/light anesthesia
  - full bladder
  - anemia
  - febrile illness/sepsis
  - drugs (e.g. atropine, cocaine, dopamine, epinephrine, ephedrine, isoflurane, isoproterenol, pancuronium) and withdrawal
  - Addisonian crisis, hypoglycemia, transfusion reaction, malignant hyperthermia
- for management of tachycardia, see *Appendices*, A33

### Intraoperative Bradycardia

- bradycardia = HR <50 bpm; most concerning are 2nd degree (Mobitz type II) and 3rd degree heart block, which can both degenerate into asystole
- causes of sinus bradycardia
  - increased parasympathetic tone vs. decreased sympathetic tone
  - must rule out hypoxemia
  - arrhythmias (see Cardiology and Cardiac Surgery, C16)
  - baroreceptor reflex due to increased ICP or increased BP
  - vagal reflex (oculocardiac reflex, carotid sinus reflex, airway manipulation)
  - drugs (e.g. suprachoroidal hemorrhage, opioids, edrophonium, neostigmine, halothane, digoxin, β-blockers)
  - high spinal/epidural anesthesia
- for management of bradycardia, see *Appendices*, A33

# Blood Pressure

## Causes of Intraoperative Hypotension/Shock

- shock: condition characterized by inability of cardiovascular system to maintain adequate end-organ perfusion and delivery of oxygen to tissues

a) hypovolemic/hemorrhagic shock
  - most common form of shock, due to decrease in intravascular volume

b) obstructive shock
  - obstruction of blood into or out of the heart
  - increased JVP, distended neck veins, increased systemic vascular resistance, insufficient cardiac output (CO)
  - e.g. tension pneumothorax, cardiac tamponade, pulmonary embolism (and other emboli – i.e. fat, air)

c) cardiogenic shock
  - increased JVP, distended neck veins, increased systemic vascular resistance, decreased CO
  - e.g. myocardial dysfunction, dysrhythmias, ischemia/infarct, cardiomyopathy, acute valvular dysfunction

d) septic shock
  - see Infectious Diseases, ID19

e) spinal/neurogenic shock
  - decreased sympathetic tone
  - hypotension without tachycardia or peripheral vasoconstriction (warm skin)

f) anaphylactic shock
  - see Emergency Medicine, ER3

g) drugs
  - vasodilators, high spinal anesthetic interfering with sympathetic outflow

h) other
  - transfusion reaction, Addisonian crisis, thyrotoxicosis, hypothyroid, aortocaval syndrome
  - see Hematology and Endocrinology

**Intraoperative Shock**

**SHOCK TED**
**S**epsis or **S**pinal shock
**H**ypovolemic/**H**emorrhagic
**O**bstructive
**C**ardiogenic
anaphylacti**K**
**T**ransfusions
**E**ndocrine (Addison's disease, hyperthryoidism)
**D**rugs

BP = CO x SVR, where CO = SV x HR
SV is a function of preload, afterload, and contractility

## Causes of Intraoperative Hypertension

- inadequate anesthesia causing pain and anxiety
- pre-existing HTN, coarctation, or preeclampsia
- hypoxemia/hypercarbia
- hypervolemia
- increased intracranial pressure
- full bladder
- drugs (e.g. ephedrine, epinephrine, cocaine, phenylephrine, ketamine) and withdrawal
- allergic/anaphylactic reaction
- hypermetabolic states: malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome, thyroid storm, pheochromocytoma (see Endocrinology, E37)

# Fluid Balance and Resuscitation

- total requirement = maintenance + deficit + ongoing loss
- in surgical settings, this formula must take into account multiple factors including pre-operative fasting/decreased fluid intake, increased losses during or before surgery, fluids given with blood products and medications
- increasingly, Enhanced Recovery After Surgery protocols recommend consumption of clear fluids up to two hours prior to surgery
- both inadequate fluid resuscitation AND excessive fluid administration increases morbidity post-operatively

## What is the Maintenance?

- average healthy adult requires approximately 2500 mL water/d
  - 200 mL/d GI losses
  - 800 mL/d insensible losses (respiration, perspiration)
  - 1500 mL/d urine (beware of renal failure)
- replacement of 'third space' losses is not warranted
- maintenance should not exceed 3ml/kg/hr
- increased requirements with fever, sweating, GI losses (vomiting, diarrhea, NG suction), adrenal insufficiency, hyperventilation, and polyuric renal disease
- decreased requirements with anuria/oliguria, SIADH, highly humidified atmospheres, and CHF
- maintenance electrolytes
  - $Na^+$: 3 mEq/kg/d
  - $K^+$: 1 mEq/kg/d
- 50 kg patient maintenance requirements
  - fluid = 40 + 20 + 30 = 90 mL/h = 2160 mL/d = 2.16 L/d
  - $Na^+$ = 150 mEq/d (therefore 150 mEq / 2.16 L/d ≈ 69 mEq/L)
  - $K^+$ = 50 mEq/d (therefore 50 mEq / 2.16 L/d ≈ 23 mEq/L)
- above patient's requirements roughly met with 2/3 D5W, 1/3 NS
  - 2/3 + 1/3 at 100 mL/h with 20 mEq KCl per litre
- 4-2-1 rule: 4 mL/h first 10 kg, 2 mL/h next 10 kg, 1 mL/h for every kg after to calculate maintenance fluid requirement
- may also add 40 kg to weight for adults to calculate maintenance fluid requirement in mL/h

### What is the Deficit?

- patients should be adequately hydrated prior to anesthesia
- total body water (TBW) = 60% or 50% of total body weight for an adult male or female, respectively (e.g. for a 70 kg adult male TBW = 70 x 0.6 = 42 L)
- total $Na^+$ content determines ECF volume; $[Na^+]$ determines ICF volume
- hypovolemia due to volume contraction
  - extra-renal $Na^+$ loss
    - GI: vomiting, NG suction, drainage, fistulae, diarrhea
    - skin/resp: insensible losses (fever), sweating, burns
    - vascular: hemorrhage
    - renal $Na^+$ and $H_2O$ loss
    - diuretics
    - osmotic diuresis
    - hypoaldosteronism
    - salt-wasting nephropathies
    - renal $H_2O$ loss
    - diabetes insipidus (central or nephrogenic)
    - hypovolemia with normal or expanded ECF volume
    - decreased CO
    - redistribution
      - hypoalbuminemia: cirrhosis, nephrotic syndrome
      - capillary leakage: acute pancreatitis, rhabdomyolysis, ischemic bowel, sepsis, anaphylaxis
- replace water and electrolytes as determined by patient's needs
- with chronic hyponatremia, correction must be done gradually over >48 h to avoid central pontine myelinolysis

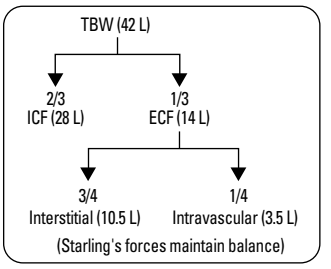



**Figure 10. Total body water division in a 70 kg adult**

**Table 4. Signs and Symptoms of Dehydration**

| Percentage of Body Water Loss | Severity | Signs and Symptoms |
|---|---|---|
| 3% | Mild | Decreased skin turgor, sunken eyes, dry mucous membranes, dry tongue, reduced sweating |
| 6% | Moderate | Oliguria, orthostatic hypotension, tachycardia, low volume pulse, cool extremities, reduced filling of peripheral veins and CVP, hemoconcentration, apathy |
| 9% | Severe | Profound oliguria or anuria and compromised CNS function with or without altered sensorium |

### What are the Ongoing Losses?

- traditionally thought that fluid loss during surgery resulted from blood loss, losses from Foley catheter, NG, surgical drains, and third spacing (sequestration of fluid into other body compartments such as GI, lung, evaporation)
- fluid therapy accounting for these losses often resulted in excess crystalloid administration
- goal-directed fluid regimens associated with lower rate of post-op complications compared to pre-determined calculations

## IV Fluids

- replacement fluids include crystalloid and colloid solutions
- IV fluids improve perfusion but NOT $O_2$ carrying capacity of blood

### Initial Distribution of IV Fluids

- $H_2O$ follows ions/molecules to their respective compartments

### Crystalloid Infusion

- salt-containing solutions that distribute only within ECF
- consensus guidelines recommend use of balanced crystalloid (i.e. Ringer's lactate) over normal saline for routine replacement and resuscitation
- maintain euvolemia in patient with blood loss: 3 mL crystalloid infusion per 1 mL of blood loss for volume replacement (i.e. 3:1 replacement)
- if large volumes are to be given, use balanced fluids such as Ringer's lactate or Plasmalyte®, as too much normal saline (NS) may lead to hyperchloremic metabolic acidosis

### Colloid Infusion

- includes protein colloids (albumin and gelatin solutions) and non-protein colloids (dextrans and starches e.g. hydroxyethol starch [HES])
- distributes within intravascular volume
- 1:1 ratio (infusion:blood loss) only in terms of replacing intravascular volume
- the use of HES solutions is controversial because of recent RCTs and meta-analyses highlighting their renal (especially in septic patients) and coagulopathic side effects, as well as a lack of specific indications for their use
  - colloids are being used based on mechanistic and experimental evidence but there is a paucity of definitive studies investigating their safety and efficacy; routine use of colloids should be avoided

**Colloids vs. Crystalloids for Fluid Resuscitation in Critically Ill People**
Cochrane DB Syst Rev 2018:CD000567
**Objectives**: To assess effect of colloids vs. crystalloids in critically ill patients on mortality, need for transfusions or renal replacement therapy, and adverse events.
**Methods**: Systematic review of RCTs and quasi-RCTs involving trauma, burns, or medical conditions (i.e. sepsis). Searched CENTRAL, MEDLINE, and Embase.
**Outcomes**: 69 studies, 30 020 participants. Starches, dextrans, albumin or FFP (moderate-certainty evidence), or gelatins (low-certainty evidence) vs. crystalloids has no difference on mortality. Starches slightly increase the need for blood transfusion (moderate-certainty evidence), and albumin or FFP may make little or no difference to the need for renal replacement therapy (low-certainty evidence). Evidence for blood transfusions for dextrans, and albumin or FFP, is uncertain.

**Table 5. IV Fluid Solutions**

| | | ECF | Ringer's Lactate | 0.9% NS | 0.45% NS in D5W | D5W | 2/3 D5W + 1/3 NS | Plasmalyte |
|---|---|---|---|---|---|---|---|---|
| mEq/L | $Na^+$ | 142 | 130 | 154 | 77 | - | 51 | 140 |
| | $K^+$ | 4 | 4 | - | - | - | - | 5 |
| | $Ca^{2+}$ | 4 | 3 | - | - | - | - | - |
| | $Mg^{2+}$ | 3 | - | - | - | - | - | 3 |
| | $Cl^-$ | 103 | 109 | 154 | 77 | - | 51 | 98 |
| | $HCO_3^-$ | 27 | 28* | - | - | - | - | 27 |
| mOsm/L | | 280-310 | 273 | 308 | 154 | 252 | 269 | 294 |
| pH | | 7.4 | 6.5 | 5.0 | 4.5 | 4.0 | 4.3 | 7.4 |

*Converted from lactate

**Table 6. Colloid HES Solutions**

| | Concentration | Plasma Volume Expansion | Duration (h) | Maximum Daily Dose (mL/kg) |
|---|---|---|---|---|
| Voluven® | 6% | 1:1 | 4-6 | 33-50 |
| Pentaspan® | 10% | 1:1.2-1.5 | 18-24 | 28 |

# Blood Products

- see Hematology, H52

# Induction

## Routine Induction vs. Rapid Sequence Induction

- routine induction is the standard in general anesthesia, however a RSI is indicated in patients at risk of regurgitation/aspiration (see *Aspiration*, A5)
- RSI uses pre-determined doses of induction drugs given in rapid succession to minimize the time patient is at risk for aspiration (e.g. from the time when they are unconscious without an ETT until the time when the ETT is in and the cuff inflated)

**Table 7. Comparison of Routine Induction vs. RSI**

| Steps | Routine Induction | RSI |
|---|---|---|
| 1. Equipment Preparation | Check equipment, drugs, suction, and monitors; prepare an alternative laryngoscope blade and a second ETT tube one size smaller, suction on | |
| 2. Pre-Oxygenation/ Denitrogenation | 100% $O_2$ for 3 min or 4-8 vital capacity breaths; reduce risk of hypoxemia during apneic period following induction | |
| 3. Pre-Treatment Agents | Use agent of choice to blunt physiologic responses to airway manipulation 3 min prior to laryngoscopy | Use agent of choice to blunt physiologic responses to airway manipulation; if possible, give 3 min prior to laryngoscopy, but can skip this step in an emergent situation |
| 4. Induction Agents | Use IV or inhalation induction agent of choice | Use pre-determined dose of fast acting induction agent of choice |
| 5. Muscle Relaxants | Muscle relaxant of choice given after the onset of the induction agent | Pre-determined dose of fast acting muscle relaxant (most commonly SCh, occasionally high dose rocuronium) given IMMEDIATELY after induction agent |
| 6. Ventilation | Bag-mask ventilation | DO NOT bag ventilate – can increase risk of aspiration |
| 7. Cricoid Pressure | Posterior pressure on thyroid cartilage to improve view of vocal cords as indicated | Traditionally Sellick maneuver, also known as cricoid pressure, to prevent regurgitation and assist in visualization (2 kg pressure with drowsiness, 3 kg with loss of consciousness) but increasingly omitted |
| 8. Intubation | Intubate, inflate cuff, confirm ETT position | Intubate once paralyzed (~45 s after SCh given), inflate cuff, confirm ETT position; cricoid pressure maintained until ETT cuff inflated and placement confirmed |
| 9. Secure Machines | Secure ETT, and begin manual/machine ventilation | |

**Calculating Acceptable Blood Losses (ABL)**

- Blood volume
  term infant 80 mL/kg
  adult male 70 mL/kg
  adult female 60 mL/kg
- Calculate estimated blood volume (EBV) (e.g. in a 70 kg male, approx. 70 mL/kg)
  EBV = 70 kg x 70 mL/kg = 4900 mL
- Decide on a transfusion trigger, i.e. the Hb level at which you would begin transfusion, (e.g. 70 g/L for a person with Hb(i) = 150 g/L)

Hb(f) = 70 g/L

- Calculate

$$ABL = \frac{Hb(Hi) - Hb(Hf)}{Hb(Hi)} \times EBV$$
$$= \frac{150 - 70}{150} \times 4900$$
$$= 2613 \text{ mL}$$

- Therefore in order to keep the Hb level above 70 g/L, RBCs would have to be given after approximately 2.6 L of blood has been lost

**Transfusion Infection Risks**

| Virus | Risk per 1 unit pRBCs |
|---|---|
| HIV | 1 in 21 million |
| Hepatitis C virus | 1 in 13 million |
| Hepatitis B virus | 1 in 7.5 million |
| HTLV | 1 in 1-1.3 million |
| Symptomatic Bacterial Sepsis | 1 in 40,000 from platelets and 1 in 250,000 from RBC |
| West Nile virus | No cases since 2003 |

Source: Callum JL, Pinkerton PH. Bloody Easy. Fourth Edition ed. Toronto: Sunnybrook and Women's College Health Science Centre; 2016

**Rocuronium versus Succinylcholine for Rapid Sequence Induction Intubation**

Cochrane DB Syst Rev 2015:CD002788.

**Objective**: Whether rocuronium creates intubating conditions comparable to those of succinylcholine during RSI intubations.

**Methods**: Systematic review of RCTs or CCTs with a dose of at least 0.6 mg/kg for rocuronium and 1 mg/kg for succinylcholine.

**Results**: 50 trials, 4151 participants. Succinylcholine was superior to rocuronium for achieving excellent intubating conditions (RR 0.86, 95% CI 0.81-0.92) and clinically acceptable intubation conditions (RR 0.97, 95% CI 0.95-0.99).

**Conclusion**: Succinylcholine created superior intubation conditions to rocuronium in achieving excellent and clinically acceptable intubating conditions.

# Induction Agents

- induction in general anesthesia may be achieved with intravenous agents, volatile inhalation agents, or both

**Solubility of Volatile Anesthetics in Blood**
**Least Soluble to Most Soluble**
Nitrous oxide < desflurane < sevoflurane < isoflurane < halothane

## Intravenous Agents

- IV induction agents are non-opioid drugs used to provide hypnosis, amnesia and blunt reflexes
- these are initially used to draw the patient into the maintenance phase of general anesthesia rapidly, smoothly and with minimal adverse effects
  - most commonly used is propofol or ketamine
  - a continuous propofol infusion may also be used for the maintenance phase of GA

**Table 8. Intravenous Induction Agents**

| | Propofol (Diprivan®) | Thiopental (sodium thiopental, sodium thiopentone)* | Ketamine (Ketalar®, Ketaject®) | Benzodiazepines (midazolam [Versed®], diazepam [Valium®], lorazepam [Ativan®]) | Etomidate |
|---|---|---|---|---|---|
| **Class** | Alkylphenol – hypnotic | Ultra-short acting thiobarbiturate – hypnotic | Phencyclidine (PCP) derivative – dissociative | Benzodiazepines – anxiolytic | Imadazole derivative - hypnotic |
| **Action** | Inhibitory at GABA synapse<br>Decreased cerebral metabolic rate and blood flow, decreased ICP, decreased SVR, decreased BP, and decreased SV | Inhibitory at GABA synapse<br>Decreased cerebral metabolism and blood flow, decreased CPP, decreased CO, decreased BP, decreased reflex tachycardia, decreased respiration | May act on NMDA (antagonistically), opiate, and other receptors<br>Increased HR, increased BP, increased SVR, increased coronary flow, increased myocardial $O_2$ uptake<br>CNS and respiratory depression, bronchial smooth muscle relaxation | Inhibitory at GABA synapse<br>Produces antianxiety and skeletal muscle relaxant effects<br>Minimal cardiac depression | Decreases concentration of GABA required to activate receptor<br>CNS depression<br>Minimal cardiac or respiratory depression |
| **Indications** | Induction<br>Maintenance<br>Total intravenous anesthesia (TIVA) | Induction<br>Control of convulsive states, obstetric patients | Major trauma, hypovolemia, obstetric bleeding, severe asthma because sympathomimetic | Used for sedation, amnesia, and anxiolysis | Induction<br>Poor cardiac function, severe valve lesions, uncontrolled hypertension |
| **Caution** | Patients who cannot tolerate sudden decreased BP (e.g fixed cardiac output or shock) | Allergy to barbiturates<br>Uncontrolled hypotension, shock, cardiac failure<br>Porphyria, liver disease, status asthmaticus, myxedema | Ketamine allergy<br>TCA medication (interaction causes HTN and dysrhythmias)<br>History of psychosis<br>Patients who cannot tolerate HTN (e.g. CHF, increased ICP, aneurysm) | Marked respiratory depression | Post-operative nausea and vomiting<br>Venous irritation |
| **Dosing** | IV induction: 2.5-3.0 mg/kg (less with opioids)<br>Unconscious <1 min<br>Lasts 4-6 min<br>t1/2 = 55 min<br>Decreased post-operative sedation, recovery time, N/V | IV induction: 3-5 mg/kg<br>Unconscious about 30 s<br>Lasts 5 min<br>Accumulation with repeat dosing – not for maintenance<br>t1/2 = 5-10 h<br>Post-operative sedation lasts hours | IV induction 1-2 mg/kg<br>Dissociation in 15 s, analgesia, amnesia, and unconsciousness in 45-60 s<br>Unconscious for 10-15 min, analgesia for 40 min, amnesia for 1-2 h<br>t1/2 = ~3 h | Onset less than 5 min if given IV<br>Duration of action long but variable/ somewhat unpredictable | IV induction 0.3 mg/kg<br>Onset 30-60 s<br>Lasts 4-8 min |
| **Special Considerations** | 0-30% decreased BP due to vasodilation<br>Reduce burning at IV site by mixing with lidocaine | Combining with rocuronium causes precipitates to form | High incidence of emergence reactions (vivid dreaming, out-of-body sensation, illusions)<br>Pretreat with glycopyrrolate to decrease salivation | Antagonist: flumazenil (Anexate®) competitive inhibitor, 0.2 mg IV over 15 s, repeat with 0.1 mg/min (max of 2 mg), t1/2 of 60 min<br>Midazolam also has amnestic (antegrade) effect and decreased risk of thrombophlebitis | Adrenal suppression after first dose, cannot repeat dose or use as infusion<br>Myoclonic movements during induction |

*As of 2011, Thiopental has been discontinued from production for North America

## Volatile Inhalational Agents

- examples include sevoflurane, desflurane, isoflurane, enflurane, halothane, and nitrous oxide

**Table 9. Volatile Inhalational Agents**

| | Sevoflurane | Desflurane | Isoflurane | Enflurane | Halothane | Nitrous oxide ($N_2O$)* |
|---|---|---|---|---|---|---|
| **MAC (% gas in $O_2$)** | 2.0 | 6.0 | 1.2 | 1.7 | 0.8 | 104 |
| **CNS** | Increased ICP | Increased ICP | Decreased cerebral metabolic rate<br>Increased ICP | ECG seizure-like activity<br>Increased ICP | Increased ICP and cerebral blood flow | — |
| **Resp** | Respiratory depression (severely decreased TV, increased RR), decreased response to respiratory $CO_2$ reflexes, bronchodilation | | | | | — |
| **CVS** | Less decrease of contractility, stable HR | Tachycardia with rapid increase in concentration | Decreased BP and CO, increased HR, theoretical chance of coronary steal** | Stable HR, decreased contractility | Decreased BP, CO, HR, and conduction<br>Sensitizes myocardium to epinephrine-induced arrhythmias | Can cause decreased HR in pediatric patients with existing heart disease |
| **MSK** | Muscle relaxation, potentiation of other muscle relaxants, uterine relaxation | | | | | |

*Properties and Adverse Effects of $N_2O$
Due to its high MAC, nitrous oxide is combined with other anesthetic gases to attain surgical anesthesia. A MAC of 104% is possible in a pressurized chamber only
Second Gas Effect
Expansion of closed spaces: closed spaces such as a pneumothorax, the middle ear, bowel lumen and ETT cuff will markedly enlarge if N20 is administered
Diffusion hypoxia: during anesthesia, the washout of $N_2O$ from body stores into alveoli can dilute the alveolar [$O_2$], creating a hypoxic mixture if the original [$O_2$] is low
**Coronary steal: isoflurane causes small vessel dilation which may compromise blood flow to areas of the heart with fixed perfusion (e.g. stents, atherosclerosis)

## MAC (Minimum Alveolar Concentration)

- the alveolar concentration of a volatile anesthetic at one atmosphere (atm) of pressure that will prevent movement in 50% of patients in response to a surgical stimulus (e.g. abdominal incision)
- potency of inhalational agents is compared using MAC
- MAC of halogenated volatile anesthetics decrease by approximately 6% per additional decade of age in adults
- 1.2-1.3 times MAC will often ablate response to stimuli in the general population
- MAC values are roughly additive when mixing $N_2O$ with another volatile agent; however, this only applies to movement, not other effects such as BP changes (e.g. 0.5 MAC of a potent agent + 0.5 MAC of $N_2O$ = 1 MAC of potent agent)
- MAC-intubation: the MAC of anesthetic that will inhibit movement and coughing during endotracheal intubation, generally 1.3 MAC
- MAC-block adrenergic response (MAC-BAR): the MAC necessary to blunt the sympathetic response to noxious stimuli, generally 1.5 MAC
- MAC-awake: the MAC of a given volatile anesthetic at which a patient will open their eyes to command, generally 0.3-0.4 of the usual MAC

**Factors increasing MAC:** chronic alcohol use, hyperthyroidism, hyperthermia, stimulant (amphetamines), young age
**Factors decreasing MAC:** acute alcohol intoxication, hypothermia, sedating drugs, advanced age, drugs (opioids, benzodiazepines)

# Muscle Relaxants and Reversing Agents

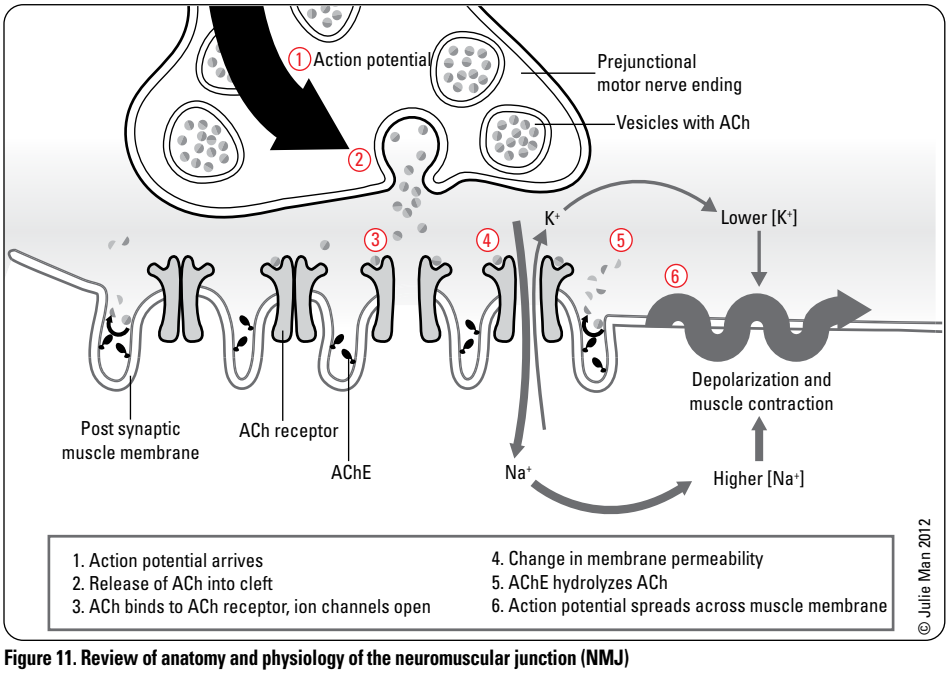



**Figure 11. Review of anatomy and physiology of the neuromuscular junction (NMJ)**

## Muscle Relaxants

- two types of muscle relaxants
  1. depolarizing muscle relaxants: succinylcholine (SCh)
  2. non-depolarizing muscle relaxants: rocuronium, mivacurium, vecuronium, cistracurium, pancuronium
- block nicotinic cholinergic receptors in NMJ
- provides skeletal muscle paralysis, including the diaphragm, but spares involuntary muscles such as the heart and smooth muscle
- never use muscle relaxants without adequate preparation and equipment to maintain airway and ventilation
- muscle relaxation produces the following desired effects:
  1. facilitates intubation
  2. assists with mechanical ventilation
  3. prevents muscle stretch reflex and decreases muscle tone
  4. allows access to the surgical field (intracavitary surgery)
- nerve stimulator (i.e. train of four) is used intraoperatively to assess the degree of nerve block; no twitch response seen with complete neuromuscular blockade

**Plasma Cholinesterase**
Plasma cholinesterase is produced by the liver and metabolizes SCh, ester local anesthetics, and mivacurium. A prolonged duration of blockade by SCh occurs with:
(a) decreased quantity of plasma cholinesterase, e.g. liver disease, pregnancy, malignancy, malnutrition, collagen vascular disease, hypothyroidism
(b) abnormal quality of plasma cholinesterase, e.g. normal levels but impaired activity of enzymes, genetically inherited

**Table 10. Depolarizing Muscle Relaxants (Non-Competitive): Succinylcholine (SCh)**

| | |
|---|---|
| **Mechanism of Action** | Mimics ACh and binds to ACh receptors causing prolonged depolarization; initial fasciculation may be seen, followed by temporary paralysis secondary to blocked ACh receptors by SCh |
| **Intubating Dose (mg/kg)** | 1-1.5 |
| **Onset** | 30-60 s – rapid (fastest of all muscle relaxants) |
| **Duration** | 3-5 min – short (no reversing agent for SCh) |
| **Metabolism** | SCh is hydrolyzed by plasma cholinesterase (pseudocholinesterase), found only in plasma and not at the NMJ |
| **Indications** | Assist intubation<br>Increased risk of aspiration (need rapid paralysis and airway control (e.g. full stomach), hiatus hernia, obesity, pregnancy, trauma)<br>Short procedures<br>Electroconvulsive therapy (ECT)<br>Laryngospasm |
| **Side Effects** | 1. SCh also stimulates muscarinic cholinergic autonomic receptors (in addition to nicotinic receptors; may cause bradycardia, dysrhythmias, sinus arrest, increased secretions of salivary glands (especially in children)<br>2. Hyperkalemia<br>Disruption of motor nerve activity causes proliferation of extrajunctional (outside NMJ) cholinergic receptors<br>Depolarization of an increased number of receptors by SCh may lead to massive release of potassium out of muscle cells<br>Patients at risk<br>3rd degree burns 24 h-6 mo after injury<br>Traumatic paralysis or neuromuscular diseases (e.g. muscular dystrophy)<br>Severe intra-abdominal infections<br>Severe closed head injury<br>Upper motor neuron lesions<br>3. Can trigger MH (see *Malignant Hyperthermia*, A28)<br>4. Increased ICP/intraocular pressure/intragastric pressure (no increased risk of aspiration if competent lower esophageal sphincter)<br>5. Fasciculations, post-operative myalgia – may be minimized if small dose of non-depolarizing agent given before SCh administration |
| **Contraindications** | |
| **Absolute** | Known hypersensitivity or allergy, positive history of malignant hyperthermia, myotonia (m. congenita, m. dystrophica, paramyotonia congenital), high risk for hyperkalemic response |
| **Relative** | Known history of plasma cholinesterase deficiency, myasthenia gravis, myasthenic syndrome, familial periodic paralysis, open eye injury |

**Table 11. Non-Depolarizing Muscle Relaxants (Competitive)**

| **Mechanism of Action** | **Competitive blockade of postsynaptic ACh receptors preventing depolarization** | | | | | |
|---|---|---|---|---|---|---|
| **Classification** | **Short** | | **Intermediate** | | **Long** | |
| | Mivacuronium | Rocuronium | Vecuronium | Cisatracurium | Pancuronium | |
| **Intubating Dose (mg/kg)** | 0.2 | 0.6-1.0 | 0.1 | 0.2 | 0.1 | |
| **Onset (min)** | 2-3 | 1.5 | 2-3 | 3 | 3-5 | |
| **Duration (min)** | 15-25 | 30-45 | 45-60 | 40-60 | 90-120 | |
| **Metabolism** | Plasma cholinesterase | Liver (major) Renal (minor) | Liver | Hofmann Eliminations | Renal (major) | Liver (minor) |
| **Indications** | Assist intubation, assist mechanical ventilation in some ICU patients, reduce fasciculations, and post-operative myalgias secondary to SCh | | | | | |
| **Side Effects** | | | | | | |
| **Histamine Release** | Yes | No | No | No | No | |
| **Other** | — | — | — | — | Tachycardia | |
| **Considerations** | Increased duration of action in renal or liver failure | Quick onset of rocuronium allows its use in rapid sequence induction<br>Cisatracurium is good for patients with renal or hepatic insufficiency | | | | Pancuronium if increased HR and BP desired |

### Reversing Agents

- sugammadex is a selective relaxant binding agent
- neostigmine, pyridostigmine, edrophonium are acetylcholinesterase inhibitors
- administer reversal agents when there has been some recovery of blockade (i.e. muscle twitch)
- can only reverse the effect of non-depolarizing muscle relaxants
- anticholinergic agents (e.g. atropine, gylcopyrrolate) are simultaneously administered to minimize muscarinic effect of reversal agents (i.e. bradycardia, salivation, increased peristalsis, and bronchoconstriction)

**Table 12. Reversal Agents for Non-Depolarizing Relaxants**

| **Agent** | **Pyridostigmine** | **Neostigmine** | **Edrophonium** | **Sugammadex** |
|---|---|---|---|---|
| **Onset** | Slow | Intermediate | Intermediate | Fast |
| **Mechanism of Action** | (acetylcholinesterase inhibitors) Inhibits enzymatic degradation of ACh, increases ACh at nicotinic and muscarinic receptors, displaces non-depolarizing muscle relaxants<br>Muscarinic effects of reversing agents include unwanted bradycardia, salivation, and increased bowel peristalsis* | | | Encapsulates and inactivates rocuronium and vecuronium → ↓ amount of agent available to bind to receptors in NMJ |
| **Dose** | 0.1-0.4 mg/kg | 0.04-0.08 mg/kg | 0.5-1 mg/kg | 2-16 mg/kg |
| **Recommended Anticholinergic** | Glycopyrrolate | Glycopyrrolate | Atropine | NA |
| **Dose of Anticholinergic (per mg)** | 0.05 mg | 0.2 mg | 0.014 mg | NA |

*Atropine and glycopyrrolate are anticholinergic agents administered to minimize muscarinic effects of reversal agents

## Analgesia

- options include opioids (e.g. morphine, fentanyl, hydromorphone), NSAIDS, acetaminophen, ketamine, gabapentin, local, and regional anesthetic (see Table 15, A25)

# Maintenance

- general anesthesia is maintained using volatile inhalation agents and/or IV agents (i.e. propofol infusion)
- analgesia (usually IV opioids) and muscle relaxants are also given as needed

# Extubation

- criteria: patient must no longer have intubation requirements
  - patency: airway must be patent
  - protection: airway reflexes intact
  - patient must be oxygenating and ventilating spontaneously
- general guidelines
  - ensure patient has normal neuromuscular function (peripheral nerve stimulator monitoring) and hemodynamic status
  - ensure patient is breathing spontaneously with adequate rate and tidal volume
  - allow ventilation (spontaneous or controlled) with 100% $O_2$ for 3-5 min
  - suction secretions from pharynx, deflate cuff, remove ETT on inspiration (vocal cords abducted)
  - ensure patient is breathing adequately after extubation
  - ensure face mask for $O_2$ delivery available
  - proper positioning of patient during transfer to recovery room (supine, head elevated)

## Complications of Extubation

- early extubation: aspiration, laryngospasm
- late extubation: transient vocal cord incompetence, edema (glottic, subglottic), pharyngitis, tracheitis

### Laryngospasm

- defined as forceful involuntary spasm of laryngeal muscles caused by stimulation of superior laryngeal nerve (by oropharyngeal secretions, blood, extubation)
- causes partial or total airway obstruction
- more likely to occur in semi-conscious patients
- prevention: extubate while patient is still deeply under anesthesia or fully awake
- treatment: apply sustained positive pressure with bag-mask ventilation with 100% $O_2$, low-dose propofol (0.5-1.0 mg/kg) optional, low-dose succinylcholine (approximately 0.25 mg/kg) and reintubate if hypoxia develops

# Regional Anesthesia

- local anesthetic agent (LA) applied around a peripheral nerve at any point along the length of the nerve (from spinal cord up to, but not including, the nerve endings) for the purpose of reducing or preventing impulse transmission
- no CNS depression (unless overdose of local anesthetic); patient remains conscious
- regional anesthetic techniques categorized as follows:
  - epidural and spinal anesthesia (neuraxial anesthesia)
  - peripheral nerve blocks
  - IV regional anesthesia (e.g. Bier block)

### Patient Preparation

- sedation and/or anxiolysis may be indicated before block
- monitoring should be as extensive as for general anesthesia

**Benefits of Regional Anesthesia**

- Reduced perioperative pulmonary complications
- Reduced perioperative analgesia requirements
- Decreased PONV
- Reduced perioperative blood loss
- Ability to monitor CNS status during procedure
- Improved perfusion
- Lower incidence of VTE
- Shorter recovery and improved rehabilitation
- Pain blockade with preserved motor function

## Epidural and Spinal Anesthesia

- most common for surgeries performed below level of umbilicus but can be extended to any level (useful in thoracic, abdominal and lower extremity surgeries). Typically placed in thoracic or lumbar spine

### Anatomy of Spinal/Epidural Area

- spinal cord extends to L2; dural sac to S2 in adults
- nerve roots (cauda equina) from L2 to S2
- needle inserted below L2 should not encounter cord, thus L3-L4, L4-L5 interspace commonly used
- structures penetrated (outside to inside)
  - skin
  - subcutaneous fat
  - supraspinous ligament
  - interspinous ligament
  - ligamentum flavum (last layer before epidural space)
  - dura + arachnoid for spinal anesthesia

**Landmarking Epidural/Spinal Anesthesia**

- Spinous processes should be maximally flexed
- L4 spinous processes found between iliac crests
- T7 landmark at the tip of the scapula

**Classic Presentation of Dural Puncture Headache**

- Onset 6 h-3 d after dural puncture
- Postural component (worse when sitting)
- Occipital or frontal localization
- ± tinnitus, diplopia

**Table 13. Epidural vs. Spinal Anesthesia**

| | Epidural | Spinal |
|---|---|---|
| **Deposition Site** | LA injected in epidural space (space between ligamentum flavum and dura)<br>Initial blockade is at the spinal roots followed by some degree of spinal cord anesthesia as LA diffuses into the subarachnoid space through the dura | LA injected into subarachnoid space in the dural sac surrounding the spinal cord and nerve roots |
| **Onset** | Significant blockade requires 10-15 min<br>Slower onset of side effects | Rapid blockade (onset in 2-5 min) |
| **Effectiveness** | Effectiveness of blockade can be variable | Very effective blockade |
| **Difficulty** | Technically more difficult; greater failure rate | Easier to perform due to visual confirmation of CSF flow |
| **Patient Positioning** | Position of patient not as important; specific gravity not an issue | Hyperbaric LA solution – position of patient important |
| **Specific Gravity/ Spread** | Epidural injections spread throughout the potential space; specific gravity of solution does not affect spread | LA solution may be made hyperbaric (of greater specific gravity than the CSF by mixing with 10% dextrose, thus increasing spread of LA to the dependent (low) areas of the subarachnoid space) |
| **Dosage** | Larger volume/dose of LA (usually > toxic IV dose) | Smaller dose of LA required (usually < toxic IV dose) |
| **Continuous Infusion** | Use of catheter allows for continuous infusion or repeat injections | None |
| **Complications** | Failure of technique<br>Hypotension<br>Bradycardia if cardiac sympathetics blocked (only if ~T2-4 block), e.g. "high spinal"<br>Epidural or subarachnoid hematoma<br>Accidental subarachnoid injection can produce spinal anesthesia (and any of the above complications)<br>Systemic toxicity of LA (accidental intravenous)<br>Catheter complications (shearing, kinking, vascular or subarachnoid placement)<br>Infection<br>Dural puncture | Failure of technique<br>Hypotension<br>Bradycardia if cardiac sympathetics blocked (only if ~T2-4 block), e.g. "high spinal"<br>Epidural or subarachnoid hematoma<br>Post-spinal headache (CSF leak)<br>Transient paresthesias<br>Spinal cord trauma<br>Infection |
| **Combined Spinal-Epidural** | Combines the benefits of rapid, reliable, intense blockade of spinal anesthesia together with the flexibility of an epidural catheter | |

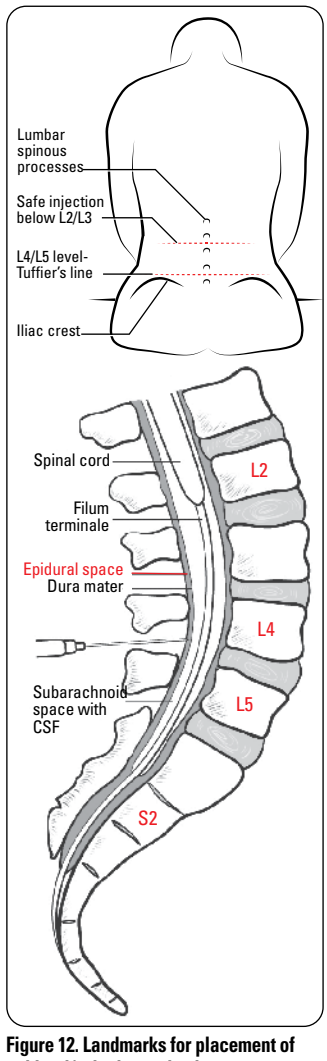



**Figure 12. Landmarks for placement of epidural/spinal anesthesia**

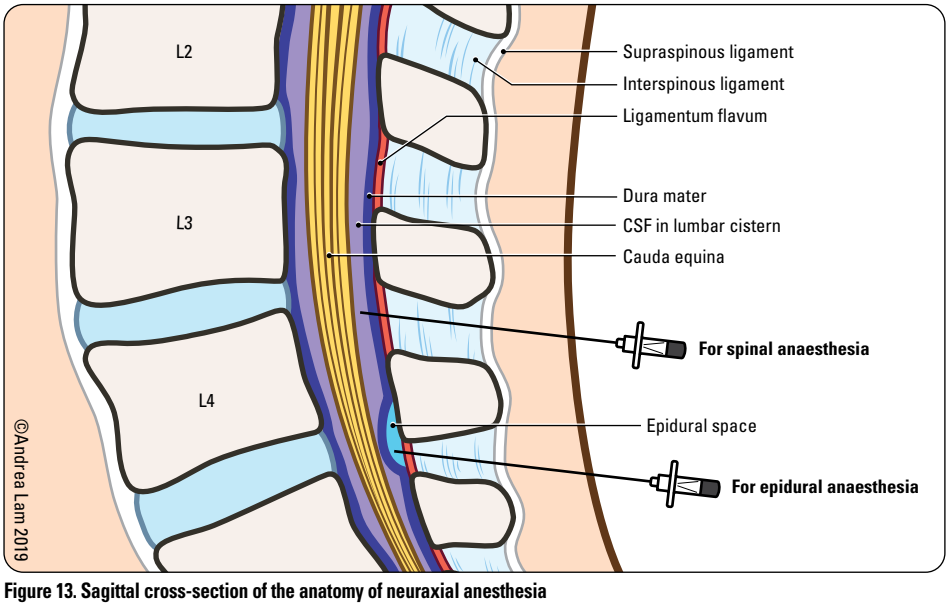



**Figure 13. Sagittal cross-section of the anatomy of neuraxial anesthesia**

## Contraindications to Spinal/Epidural Anesthesia

- absolute contraindications
  - lack of resuscitative drugs/equipment
  - patient refusal
  - allergy to local anesthetic
  - infection at puncture site or underlying tissues
  - coagulopathies/bleeding diathesis
  - raised ICP
  - sepsis/bacteremia
  - severe hypovolemia
  - cardiac lesion with fixed output states (severe mitral/aortic stenosis)
  - lack of IV access

- relative contraindications
  - pre-existing neurological disease (demyelinating lesions)
  - previous spinal surgery, severe spinal deformity
  - prolonged surgery
  - major blood loss or maneuvers that can compromise reaction

## Peripheral Nerve Blocks

- deposition of LA around the target nerve or plexus
- ultrasound guidance and peripheral nerve stimulation (needle will stimulate target nerve/plexus) may be used to guide needle to target nerve while avoiding neural trauma or intraneural injection
- most major nerves or nerve plexi can be targeted (brachial plexus block, femoral nerve block, sciatic nerve block, etc.)
- performed with standard monitors
- approximately 2-4 per 10,000 risk of late neurologic injury
- resuscitation equipment must be available

### Contraindications to Peripheral Nerve Blockade

- absolute contraindications
  - allergy to LA
  - patient refusal
- relative contraindications
  - certain types of pre-existing neurological dysfunction (e.g. ALS, MS, diabetic neuropathy)
  - local infection at block site
  - bleeding disorder

# Local Anesthesia

## Local Anesthetic Agents

- see Table 14, A22, for list of LA agents

### Definition and Mode of Action

- LA are drugs that block the generation and propagation of impulses in excitable tissues: nerves, skeletal muscle, cardiac muscle, brain
- LA bind to receptors on the cytosolic side of the $Na^+$ channel, inhibiting $Na^+$ flux and thus blocking impulse conduction
- different types of nerve fibres undergo blockade at different rates

### Absorption, Distribution, Metabolism

- LA readily crosses the blood-brain barrier (BBB) once absorbed into the bloodstream
- ester-type LA (e.g. procaine, tetracaine) are broken down by plasma and hepatic esterases; metabolites excreted via kidneys
- amide-type LA (lidocaine, bupivicaine) are broken down by hepatic mixed-function oxidases (P450 system); metabolites excreted via kidneys

### Selection of LA

- choice of LA depends on:
  - onset of action: influenced by pKa (the lower the pKa, the higher the concentration of the base form of the LA, and the faster the onset of action)
  - duration of desired effects: influenced by protein binding (longer duration of action when protein binding of LA is strong)
  - potency: influenced by lipid solubility (agents with high lipid solubility penetrate the nerve membrane more easily)
  - unique needs (e.g. sensory blockade with relative preservation of motor function by bupivicaine at low doses)
  - potential for toxicity

**Table 14. Local Anesthetic Agents**

| | Maximum Dose | Maximum Dose with Epinephrine | Potency | Duration | Onset |
|---|---|---|---|---|---|
| chloroprocaine | 11 mg/kg | 14 mg/kg | Low | 15-30 min | Fast |
| lidocaine | 5 mg/kg | 7 mg/kg | Medium | 1-2 h | Fast |
| bupivacaine | 2.5 mg/kg | 3 mg/kg | High | 3-8 h | Slow |
| ropivacaine | 2.5 mg/kg | 3 mg/kg | High | 2-8 h | Medium |
| mepivacaine | 5 mg/kg | 7 mg/kg | Medium | 3-6 h | Fast |

# Systemic Toxicity

- see Table 14, A22 for maximum doses, potency, and duration of action for common LA agents
- occurs by accidental intravascular injection, LA overdose, or unexpectedly rapid absorption

### CNS Effects
- CNS effects first appear to be excitatory due to initial block of inhibitory fibres, then subsequent block of excitatory fibres
- effects in order of appearance
  - numbness of tongue, perioral tingling, metallic taste
  - disorientation, drowsiness
  - tinnitus
  - visual disturbances
  - muscle twitching, tremors
  - unconsciousness
  - convulsions, seizures
  - generalized CNS depression, coma, respiratory arrest

### CVS Effects
- vasodilation, hypotension
- decreased myocardial contractility
- dose-dependent delay in cardiac impulse transmission
  - prolonged PR, QRS intervals
  - sinus bradycardia
- CVS collapse

### Treatment of Systemic Toxicity
- early recognition of signs; get help
- 100% $O_2$, manage ABCs
- diazepam or other anticonvulsant to prevent potential onset of seizures
- manage arrhythmias
- Intralipid® 20% to bind local anesthetic in circulation

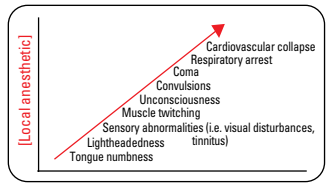



**Figure 14. Local anesthetic systemic toxicity**

# Local Infiltration and Hematoma Blocks

### Local Infiltration
- injection of tissue with LA, producing a lack of sensation in the infiltrated area due to LA acting on nerves
- suitable for small incisions, suturing, excising small lesions
- can use fairly large volumes of dilute LA to infiltrate a large area
- low concentrations of epinephrine (1:100,000-1:200,000) cause vasoconstriction, thus reducing bleeding and prolonging the effects of LA by reducing systemic absorption

**Where Not to Use LA with Epinephrine**
"Ears, Fingers, Toes, Penis, Nose"

### Fracture Hematoma Block
- special type of local infiltration for pain control during manipulation of certain fractures
- hematoma created by fracture is infiltrated with LA to anesthetize surrounding tissues
- sensory blockade may only be partial
- no muscle relaxation

# Topical Anesthetics

- various preparations of local anesthetics available for topical use, may be a mixture of agents (EMLA cream is a combination of 2.5% lidocaine and prilocaine)
- must be able to penetrate the skin or mucous membrane

# Post-Operative Care

- pain management should be continuous from OR to post-anesthetic care unit (PACU) to hospital ward and home

# Common Post-Operative Anesthetic Complications

### Uncontrolled/Poorly Controlled Pain

### Nausea and Vomiting
- hypotension and bradycardia must be ruled out
- pain and surgical manipulation also cause nausea
- often treated with dimenhydrinate (Gravol®), metoclopramide (Maxeran®; not with bowel obstruction), prochlorperazine (Stemetil®), ondansetron (Zofran®), granisetron (Kytril®)

### Confusion and Agitation
- ABCs first – confusion or agitation can be caused by airway obstruction, hypercapnea, hypoxemia
- neurologic status (Glasgow Coma Scale, pupils), residual paralysis from anesthetic
- pain, distended bowel/bladder
- fear/anxiety/separation from caregivers, language barriers
- metabolic disturbance (hypoglycemia, hypercalcemia, hyponatremia – especially post-TURP)
- intracranial cause (stroke, raised ICP)
- drug effect (ketamine, anticholinergics, serotonin)
- elderly patients are more susceptible to post-operative delirium

### Respiratory Complications
- susceptible to aspiration of gastric contents due to PONV and unreliable airway reflexes
- airway obstruction (secondary to reduced muscle tone from residual anesthetic, soft tissue trauma and edema, or pooled secretions) may lead to inadequate ventilation, hypoxemia, and hypercapnia
- airway obstruction can often be relieved with head tilt, jaw elevation, and anterior displacement of the mandible. If the obstruction is not reversible, a nasal or oral airway may be used

### Hypotension
- must be identified and treated quickly to prevent inadequate perfusion and ischemic damage
- reduced cardiac output (hypovolemia, most common cause) and/or peripheral vasodilation (residual anesthetic agent)
- first step in treatment is usually the administration of fluids ± inotropic agents

### Hypertension
- pain, hypercapnia, hypoxemia, increased intravascular fluid volume, and sympathomimetic drugs can cause hypertension
- IV nitroglycerin, hydralazine, calcium channel blockers or β-blocking drugs (e.g. esmolol and metoprolol) can be used to treat hypertension

**Risk Factors for Post-Operative Nausea and Vomiting (PONV)**
- Young age
- Female
- History of PONV
- Non-smoker
- Type of surgery: ophtho, ENT, abdo/pelvic, plastics
- Type of anesthetic: $N_2O$, opioids, volatile agents

**Dexamethasone versus Standard Treatment for Postoperative Nausea and Vomiting in Gastrointestinal Surgery: Randomised Controlled Trial (DREAMS Trial)**
BMJ 2017;357:j1455
**Objectives**: Whether preoperative dexamethasone reduces postoperative vomiting in patients undergoing elective bowel surgery and whether it is associated with other measurable benefits during recovery from surgery.
**Method**: Pragmatic two arm parallel group randomised trial with blinded postoperative care and outcome assessment.
**Results**: Patients receiving additional 8 mg of IV dexamethasone at induction is associated with lower rates of vomiting within 24 hours of surgery (NNT=13) and reduced need for antiemetics up to 72h (NNT=8) vs. standard of care.
**Conclusions**: A single dose of dexamethasone at induction of anesthesia significantly reduces incidence of PONV and need for rescue antiemetics post-operatively with no increase in adverse events.

# Pain Management

### Definitions
- pain: perception of nociception, which occurs in the brain
- nociception: detection, transduction, and transmission of noxious stimuli

### Pain Classifications
- temporal: acute vs. chronic
- mechanism: nociceptive vs. neuropathic

## Acute Pain
- pain of short duration (<6 wk) usually associated with surgery, trauma, or acute illness; often associated with inflammation
- usually limited to the area of damage/trauma and resolves with healing

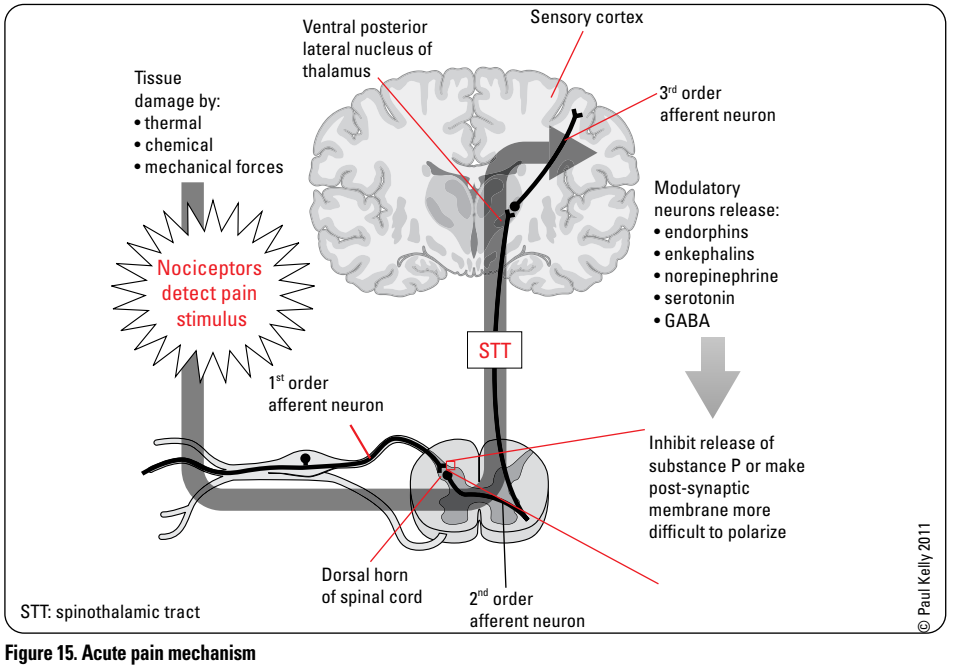



Figure 15. Acute pain mechanism

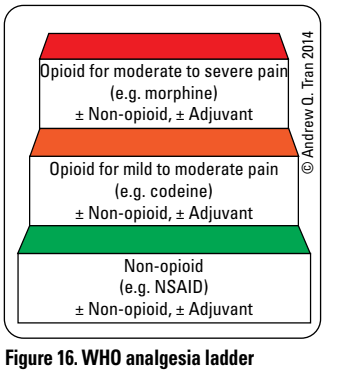



Figure 16. WHO analgesia ladder

## Pharmacological Management of Acute Pain

- ask the patient to rate the pain out of 10, or use visual analog scale, to determine severity
- pharmacological treatment guided by WHO analgesia ladder
- patient controlled analgesia (PCA)
  - involves the use of computerized pumps that can deliver a constant infusion and bolus breakthrough doses of parenterally-administered opioid analgesics
  - limited by lockout intervals
  - most commonly used agents: morphine and hydromorphone
  - see Table 17, A26 for suggested infusion rate, PCA dose and lockout intervals

### Table 15. Commonly Used Analgesics

| | Acetaminophen | NSAIDs | Opioids |
|---|---|---|---|
| **Examples** | Tylenol® | Aspirin®, ibuprofen, naproxen, ketorolac (IV) | Oral: codeine, oxycodone, morphine, hydromorphone<br>Parenteral: morphine, hydromorphone, fentanyl |
| **Indications** | First-line for mild acute pain | Mild-moderate pain | Oral: moderate acute pain<br>Parenteral: moderate-severe acute pain |
| **Mechanism of Action** | Unclear, hypothesized cyclooxygenase-2 (COX-2) inhibition<br>Unclear, hypothesized modulation of endogenous cannabinoid system | Non-selective COX-1 and 2 inhibition reducing proinflammatory prostaglandin synthesis | Dampens nociceptive transmission between 1st and 2nd order neurons in the dorsal horn<br>Activates ascending modulatory pathways resulting in release of inhibitory neurotransmitters<br>Inhibits peripheral inflammatory response and hyperalgesia<br>Affects mood and anxiety – alleviates the affective component of perceived pain |
| **Dosing/Administration** | Limited by analgesic ceiling beyond which there is no additional analgesia<br>Opioid-sparing<br>Max dose of 4 g/24 h | Limited by analgesic ceiling beyond which there is no additional analgesia<br>Opioid-sparing<br>Significant inter-individual variation in efficacy | No analgesic ceiling (except for codeine)<br>Can be administered intrathecally (spinal block) or by continuous infusion |
| **Side Effects/Toxicity** | Considered relatively safe<br>Liver toxicity in elevated doses | Gastric ulceration/bleeding<br>Decreased renal perfusion<br>Photosensitivity<br>Premature closure of the ductus arteriosus in pregnancy | Respiratory depression<br>Constipation and abdominal pain<br>Sedation<br>N/V<br>Pruritus<br>Confusion (particularly in the elderly)<br>Dependence |

### Table 16. Opioids

| Agent | Relative Dose to 10 mg Morphine IV | Moderate Dose | Onset | Duration | Special Considerations |
|---|---|---|---|---|---|
| **Codeine** | 200 mg PO | 15-30 mg PO | Late (30-60 min) | Moderate (4-6 h) | Primarily post-operative use, not for IV use. Not ideal as analgesic effect depends on highly variable CYP2D6 metabolism |
| **Meperidine (Demerol®)** | 75 mg IV | 2-3 mg/kg IV | Moderate (10 min) | Moderate (2-4 h) | Anticholinergic, hallucinations, less pupillary constriction than morphine, metabolite build up may cause seizures<br>Decreased use for pain management due to potential toxicity compared to other opioids. Typically reserved to treat post-operative shivering. Absolute contraindication in patients taking MAO-inhibitors |
| **Morphine** | 10 mg IV<br>20 mg PO | 0.2-0.3 mg/kg IV<br>0.4-0.6 mg/kg PO | Moderate (5-10 min) | Moderate (4-5 h) | Histamine release leading to decrease in BP |
| **Oxycodone Controlled Release (Oxyneo®)** | 15 mg PO | 10-20 mg PO (no IV) | Late (30-45 min) | Long (8-12 h) | Do not split, crush, or chew tablet (but can be difficult to swallow) |
| **Oxycodone Regular Tablet (Oxy IR®)** | 15 mg PO (no IV) | 5-15 mg PO | Moderate (15 min) | Moderate (3-6 h) | Percocet® = oxycodone 5 mg + acetaminophen 325 mg |
| **Hydromorphone (Dilaudid®)** | 2 mg IV<br>10 mg PO | 40-60 µg/kg IV<br>2-4 mg PO | Moderate (15 min) | Moderate (4-5 h) | Less pruritus, N&V, and sedation compared to morphine |
| **Fentanyl** | 100 µg IV | 2-3 µg/kg IV | Rapid (<5 min) | Short (0.5-1 h) | Transient muscle rigidity in very high doses |

**Cautionary Use of NSAIDs in Patients with**
- Asthma
- Coagulopathy
- GI ulcers
- Renal insufficiency
- Pregnancy, 3rd trimester

**Opioid Conversion**

| | Parenteral (IV) | Equivalent Oral Dose |
|---|---|---|
| Morphine | 10 mg | 30 mg |
| Hydromorphone | 2 mg | 4 mg |
| Codeine | 120 mg | 200 mg |
| Oxycodone | | N/A |
| 20 mg | | |
| Fentanyl IV | | 100 µg |
| N/A | | |

**Common Side Effects of Opioids**
- N/V
- Constipation
- Sedation
- Pruritus
- Abdominal pain
- Urinary retention
- Respiratory depression

When prescribing opioids, consider:
- Breakthrough dose
- Anti-emetics
- Laxative

**PCA Parameters**
- Loading dose
- Bolus dose
- Lockout interval
- Continuous infusion (optional)
- Maximum 4 h dose (limit)

**Advantages of PCA**
- Improved patient satisfaction
- Fewer side effects
- Accommodates patient variability
- Accommodates changes in opioid requirements

**Patient Controlled Opioid Analgesia versus Non-Patient Controlled Opioid Analgesia for Postoperative Pain**
Cochrane DB Syst Rev 2015:CD003348
**Purpose**: To evaluate the efficacy of patient controlled analgesia (PCA) versus non-patient controlled opioid analgesia of as-needed opioid analgesia for postoperative pain relief.
**Methods**: Meta-analyses of RCTs comparing PCA vs. conventional administration of opioid analgesia. Assessment employed a visual analog scale (VAS) for pain intensity along with overall analgesic consumption, patient satisfaction, length of stay, and adverse side effects.
**Results**: 49 studies with a total of 1725 patients receiving PCA and 1687 patients assigned to a control group. PCA had a lower VAS pain intensity score vs. non-patient controlled analgesia over most time intervals in the first 48h. PCA was associated with higher patient satisfaction and consumed higher amounts of opioids than controls. PCA was also associated with higher incidence of pruritus but not other adverse events.
**Conclusions**: Moderate to low quality evidence that PCA is an efficacious alternative to non-patient controlled systemic analgesia for postoperative pain control.

**Table 16. Opioids** (continued)

| Agent | Relative Dose to 10 mg Morphine IV | Moderate Dose | Onset | Duration | Special Considerations |
|---|---|---|---|---|---|
| **Remifentanil** | 100 µg IV | 0.5-1.5 µg/kg IV | Rapid (1-3 min) | Ultra short (<10 min) | Only use during induction and maintenance of anesthesia |
| **Methadone (opioid agonist)** | Morphine to methadone conversion is variable based on patient's morphine dose. Ranges from 1/4 to 1/20 | 15-40 mg/d in divided doses | Rapid (8 min) | 15-90 (24h average) | Can only be prescribed by federally/provincially licensed physicians<br>Acts through both NMDA and mu receptors<br>Challenging due to variable equianalgesic dose and half-life<br>After titration, accumulates in tissue for once/twice daily dosing<br>Metabolized by CYP3A4<br>Caution with high doses, may cause QT prolongation, baseline ECG required |
| **Buprenorphine (opioid agonist antagonist)** | Varies depending on route of administration (pill/film, transdermal) | Film: 2 mg up to max of 24 mg | Moderate (30 min) | 6-8 h | For moderate to severe chronic pain and opioid addiction<br>Ceiling effect for respiratory depression but not analgesia<br>High affinity to mu-opioid receptors, very resistant to reversal with opioid antagonists |

In general, parenteral route is 2-3x more potent than oral

**Table 17. Opioid PCA Doses**

| Agent | PCA Dose | PCA Lockout Interval | PCA 4 h Maximum |
|---|---|---|---|
| Morphine | 1 mg | 5 min | 30 mg |
| Hydromorphone | 0.2 mg | 5 min | 6 mg |
| Fentanyl | 25-50 µg | 5 min | 400 µg |

### Opioid Antagonists (naloxone, naltrexone)

- indication: opioid overdose (manifests primarily at CNS, e.g. respiratory depression)
- mechanism of action: competitively inhibit opioid receptors, predominantly µ receptors
  - naloxone is short-acting (t1/2 = 1 h); effects of narcotic may return when naloxone wears off; therefore, the patient must be observed closely following its administration
  - naltrexone is longer-acting (t1/2 = 10 h); less likely to see return of opioid effects
- side effects: relative overdose of naloxone may cause nausea, agitation, sweating, tachycardia, hypertension, re-emergence of pain, pulmonary edema, seizures (essentially opioid withdrawal)

## Neuropathic Pain

- see Neurology, N41

## Chronic Pain

- chronic pain: greater than 3 mo, or recurrent pain that occurs at least 3 times throughout 3 mo period
- pain of duration or intensity that persists beyond normal tissue healing and adversely affects functioning
- in the perioperative period, consider continuing regular long-acting analgesics and augmenting with regional techniques, adjuvants, additional opioid analgesia and non-pharmacological techniques

### Central Sensitization

- central sensitization: hyperalgesia (increased sensitivity to pain) as a result of central nervous system mechanisms
- may have nociceptive and neuropathic components; dysregulation of analgesic pathways implicated
- plays a role in fibromyalgia

### Chronic Post-Surgical Pain

- chronic post-surgical pain (CPSP): pain that develops after surgery and persists for at least 2 mo
- primary predictor of CPSP is history of chronic pain; other risk factors include female gender, surgical procedure/approach, poor social supports, catastrophizing behaviour



**Epidural versus Non-Epidural or No Analgesia for Pain Management in Labour**
Cochrane DB Syst Rev 2018:CD000331
**Objectives**: To assess effectiveness and safety of all types of epidural analgesia when compared with non-epidural or no pain relief during labour.
**Methods**: Systematic review of RCTs comparing epidural with any form of pain relief not involving regional blockade, or no pain relief in labour.
**Results**: 52 studies involving over 11000 women were included; 34 studies compared epidural analgesia with opioids. Epidural analgesia was associated with lower pain intensity, higher satisfaction, and decreased need for additional pain relief vs. opioids. While it was also associated with increased risk of assisted vaginal birth (RR 1.44, 95% CI 1.29-1.60), post-hoc analysis of studies conducted after 2005 eliminates this risk (RR 1.19, 95% CI 0.97-1.46). Women with epidural experienced more hypotension, motor blockage, fever, and urinary retention with less risk of respiratory depression and nausea/vomiting. There was no difference in neonatal outcomes, admission to NICU, caesarean section rates, or maternal long-term backache.
**Conclusions**: Epidural analgesia may be more effective in reducing pain during labour and increasing maternal satisfaction than non-epidural methods and, when considering modern approaches, is not associated with increased instrumentation. Epidural analgesia had no impact on the risk of caesarean section or long-term backache, and did not appear to have an immediate effect on neonatal status as determined by Apgar scores or in admissions to NICU.



**Nociceptive Pathways in Labour and Delivery**

**Labour**
- Cervical dilation and effacement stimulates visceral nerve fibres entering the spinal cord at T10-L1

**Delivery**
- Distention of lower vagina and perineum causes somatic nociceptive impulses via the pudendal nerve entering the spinal cord at S2-S4

# Obstetrical Anesthesia

## Anesthesia Considerations in Pregnancy

- airway
  - possible difficult airway as tissues becomes edematous and friable especially in labour
- respiratory
  - decreased FRC and increased $O_2$ consumption cause more rapid desaturation during apnea
- cardiovascular system
  - increased blood volume > increased RBC mass results in mild anemia
  - decreased SVR proportionately greater than increased CO results in decreased BP
  - prone to decreased BP due to aortocaval compression (supine hypotensive syndrome) – therefore for surgery, a pregnant patient is positioned in left uterine displacement (approximately 15°C) using a wedge under her right flank
- central nervous system
  - decreased MAC due to hormonal effects
  - increased block height due to engorged epidural veins
- gastrointestinal system
  - delayed gastric emptying
  - increased volume and acidity of gastric fluid
  - decreased LES tone
  - increased abdominal pressure
  - combined, these lead to an increased risk of aspiration – therefore for surgery, a pregnant patient is given sodium citrate 30 cc PO immediately before surgery to neutralize gastric acidity

## Options for Analgesia during Labour

- psychoprophylaxis – Lamaze method
  - patterns of breathing and focused attention on fixed object
- systemic medication
  - easy to administer, but risk of maternal or neonatal respiratory depression
  - opioids most commonly used if delivery is not expected within 4 h; fentanyl can be considered
- inhalational analgesia
  - easy to administer, makes uterine contractions more tolerable, but does not relieve pain completely
  - 50% nitrous oxide is insufficient alone but good safety profile for mother + child
- neuraxial anesthesia
  - provides excellent analgesia with minimal depressant effects
  - hypotension is the most common complication
  - maternal BP monitored q2-5min for 15-20 min after initiation and regularly thereafter
  - epidural usually given as it preferentially blocks sensation, leaving motor function intact

## Options for Caesarean Section

- neuraxial: spinal or epidural
- general: used if contraindications or time precludes regional blockade (see *Regional Anesthesia, Epidural and Spinal Anesthesia*, A20)

# Pediatric Anesthesia

## Respiratory System

- in comparison to adults, anatomical differences in infants include:
  - large head, short trachea/neck, large tongue, larynx positioned more superior and anterior, adenoids, and tonsils
  - narrow nasal passages (obligate nasal breathers until 5 mo)
  - narrowest part of airway at the level of the cricoid vs. glottis in adults
  - epiglottis is longer, U shaped and angled at 45°; carina is wider and is at the level of T2 (T4 in adults)
- physiologic differences include:
  - faster RR, immature respiratory centres which are depressed by hypoxia/hypercapnea (airway closure occurs in the neonate at the end of expiration)
  - less oxygen reserve during apnea – decreased total lung volume, vital and functional reserve capacity together with higher metabolic needs
  - greater V/Q mismatch – lower lung compliance due to immature alveoli (mature at 8 yr)
  - greater work of breathing – greater chest wall compliance, weaker intercostals/diaphragm, and higher resistance to airflow

## Cardiovascular System

- blood volume at birth is approximately 80 mL/kg; transfusion should be started if >10% of blood volume is lost
- children have a high HR and low BP
- CO is dependent on HR, not stroke volume because of low heart wall compliance; therefore, bradycardia severe compromise in CO

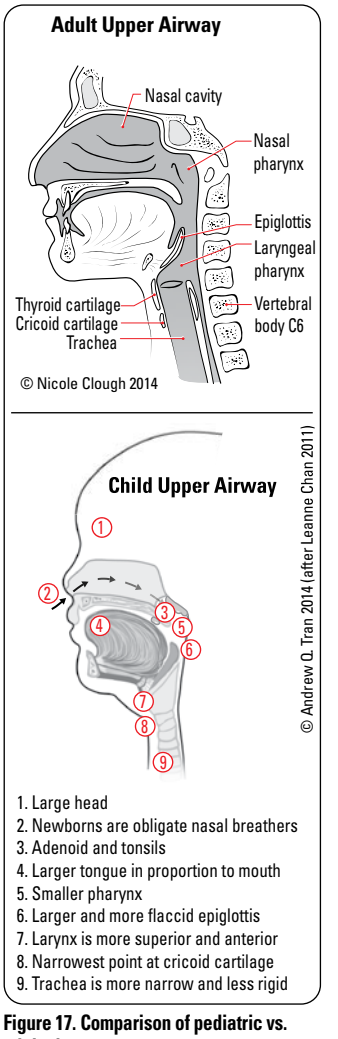



**Figure 17. Comparison of pediatric vs. adult airway**

**To increase alveolar minute ventilation in neonates, increase respiratory rate, not tidal volume**
Neonate: 30-40 breaths/min
Age 1-13: (24 – [age/2]) breaths/min

**ETT Sizing in Pediatrics**
Diameter (mm) of tracheal tube in children after 1 year = (age/4) + 4
Length (cm) of tracheal tube = (age/2) + 12

### Temperature Regulation
- vulnerable to hypothermia
- minimize heat loss by use of warming blankets, covering the infant's head, humidification of inspired gases, and warming of infused solutions

### Central Nervous System
- MAC of halothane is increased compared to the adult (0.75% adult, 1.2% infant, 0.87% neonate)
- NMJ is immature for the first 4 wk of life and thus there is an increased sensitivity to non-depolarizing relaxants
- parasympathetics mature at birth, sympathetics mature at 4-6 mo; thus, there is an autonomic imbalance
- infant brain is 12% of body weight and receives 34% of CO (adult: 2% body weight and 14% CO)

### Glucose Maintenance
- infants <1 yr can become seriously hypoglycemic during pre-operative fasting and post-operatively if feeding is not recommenced as soon as possible
- after 1 yr, children are able to maintain normal glucose homeostasis in excess of 8 h

### Pharmacology
- higher dose requirements because of higher TBW (75% vs. 60% in adults) and greater volume of distribution
- barbiturates/opioids more potent due to greater permeability of BBB
- muscle relaxants
  - non-depolarizing
    - immature NMJ, variable response
  - depolarizing
    - must pre-treat with atropine or may experience profound bradycardia and/or sinus node arrest due to PNS > SNS (also dries oral secretions)
    - more susceptible to arrhythmias, hyperkalemia, rhabdomyolysis, myoglobinemia, masseter spasm and malignant hyperthermia

# Uncommon Complications

## Malignant Hyperthermia

- hypermetabolic disorder of skeletal muscle
- due to an uncontrolled increase in intracellular $Ca^{2+}$ (because of an anomaly of the ryanodine receptor which regulates $Ca^{2+}$ channel in the sarcoplasmic reticulum of skeletal muscle)
- autosomal dominant inheritance
- incidence of 1-5 in 100,000, may be associated with skeletal muscle abnormalities such as dystrophy or myopathy
- anesthetic drugs triggering MH include:
  - all inhalational agents except nitrous oxide
  - depolarizing muscle relaxants: SCh



**Signs of Malignant Hyperthermia**
- Unexplained rise in $ETCO_2$
- Increase in minute ventilation
- Tachycardia
- Rigidity
- Hyperthermia (late sign)

### Clinical Picture
- onset: immediate or hours after contact with trigger agent
  - increased oxygen consumption
  - increased $ETCO_2$ on capnograph
  - tachycardia/dysrhythmia
  - tachypnea/cyanosis
  - diaphoresis
  - hypertension
  - increased temperature (late sign)
- muscular symptoms
  - trismus (masseter spasm) common but not specific for MH (occurs in 1% of children given SCh with halothane anesthesia)
  - tender, swollen muscles due to rhabdomyolysis
  - trunk or total body rigidity

### Complications
- coma
- DIC
- rhabdomyolysis
- myoglobinuric renal failure/hepatic dysfunction
- electrolyte abnormalities (e.g. hyperkalemia) and secondary arrhythmias
- ARDS
- pulmonary edema
- can be fatal if untreated

### Prevention

- suspect MH in patients with a family history of problems/death with anesthetic
- avoid all trigger medications, use vapour free equipment, use regional anesthesia if possible
- central body temp and $ETCO_2$ monitoring

### Malignant Hyperthermia Management

(Based on Malignant Hyperthermia Association of the U.S. [MHAUS] Guidelines, 2008)

1. notify surgeon, discontinue volatile agents and succinylcholine, hyperventilate with 100% oxygen at flows of 10 L/min or more, halt the procedure as soon as possible
2. dantrolene 2.5 mg/kg IV, through large-bore IV if possible
   - repeat until there is control of signs of MH; up to 30 mg/kg as necessary
3. bicarbonate 1-2 mEq/kg if blood gas values are not available for metabolic acidosis
4. cool patients with core temperature >39°C
   - lavage open body cavities, stomach, bladder, rectum; apply ice to surface; infuse cold saline IV
   - stop cooling if temperature is <38°C to prevent drift to <36°C
5. dysrhythmias usually respond to treatment of acidosis and hyperkalemia
   - use standard drug therapy except $Ca^{2+}$ channel blockers as they may cause hyperkalemia and cardiac arrest in presence of dantrolene
6. hyperkalemia
   - treat with hyperventilation, bicarbonate, glucose/insulin, calcium
   - bicarbonate 1-2 mEq/kg IV, calcium chloride 10 mg/kg or calcium gluconate 10-50 mg/kg for life-threatening hyperkalemia and check glucose levels hourly
7. follow $ETCO_2$, electrolytes, blood gases, creatine kinase (CK), core temperature, urine output/colour with Foley catheter, coagulation studies
   - if CK and/or potassium rises persistently or urine output falls to <0.5 mL/kg/h, induce diuresis to >1 mL/kg/h urine to avoid myoglobinuric renal failure
8. maintain anesthesia with benzodiazepines, opioids, and propofol
9. transfer to ICU bed



**Basic Principles of MH Management**

**"Some Hot Dude Better Get Iced Fluids Fast"**
**S**top all triggering agents, give 100% $O_2$
**H**yperventilate
**D**antrolene 2.5 mg/kg every 5 min
**B**icarbonate
**G**lucose and insulin
**I**V fluids; cool patient to 38°C
**F**luid output; consider furosemide
**F**ast Heart [tachycardia]; be prepared to treat VT

## Abnormal Pseudocholinesterase

- pseudocholinesterase hydrolyzes SCh and mivacurium
- individuals with abnormal pseudocholinesterase will have prolonged muscular blockade
- SCh and mivacurium are contraindicated in those with abnormal pseudocholinesterase
- if SCh or mivacurium are given accidentally, treat with mechanical ventilation until function returns to normal (do not use cholinesterase inhibitors as it will cause rebound neuromuscular blockade once cholinesterase inhibitor effect is terminated)

# Appendices

## Difficult Tracheal Intubation in Unconscious Patient

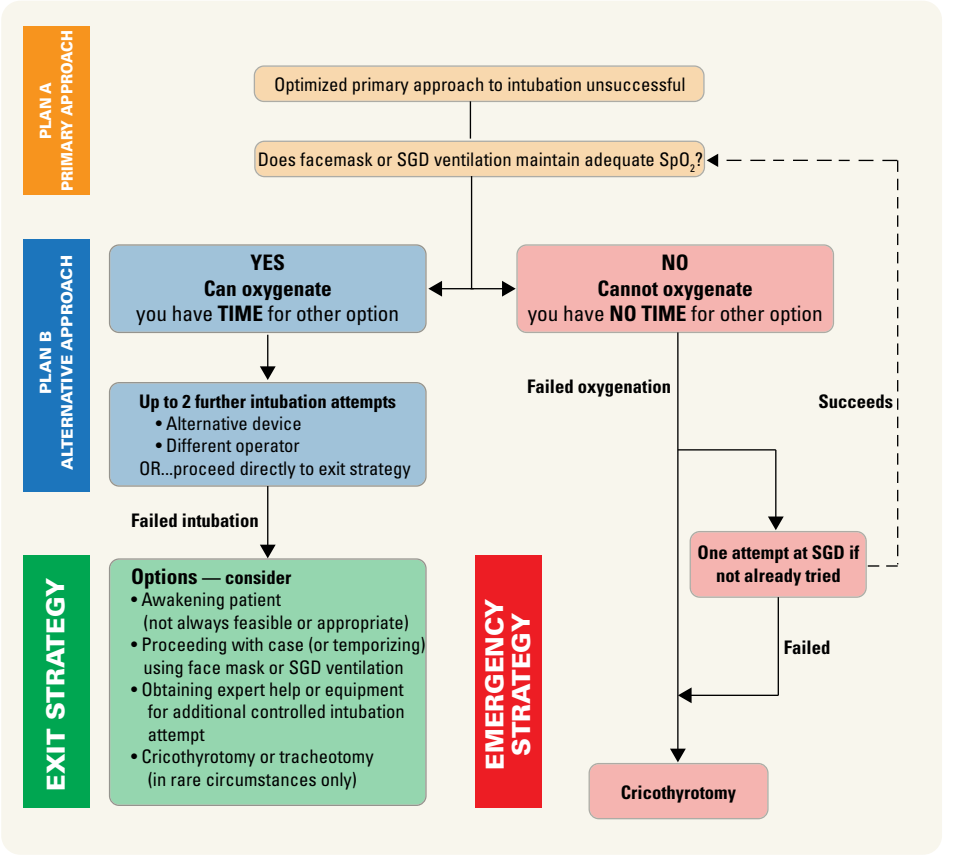



**Figure 18. Difficult tracheal intubation encountered in the unconscious patient**
SGD = supraglottic device

Reprinted with permission. Law JA, et al. The difficult airway with recommendations for management – Part 1 – Difficult tracheal intubation encountered in an unconscious/induced patient. Can J Anesth 2013;60:1089–1118.

# Difficult Tracheal Intubation

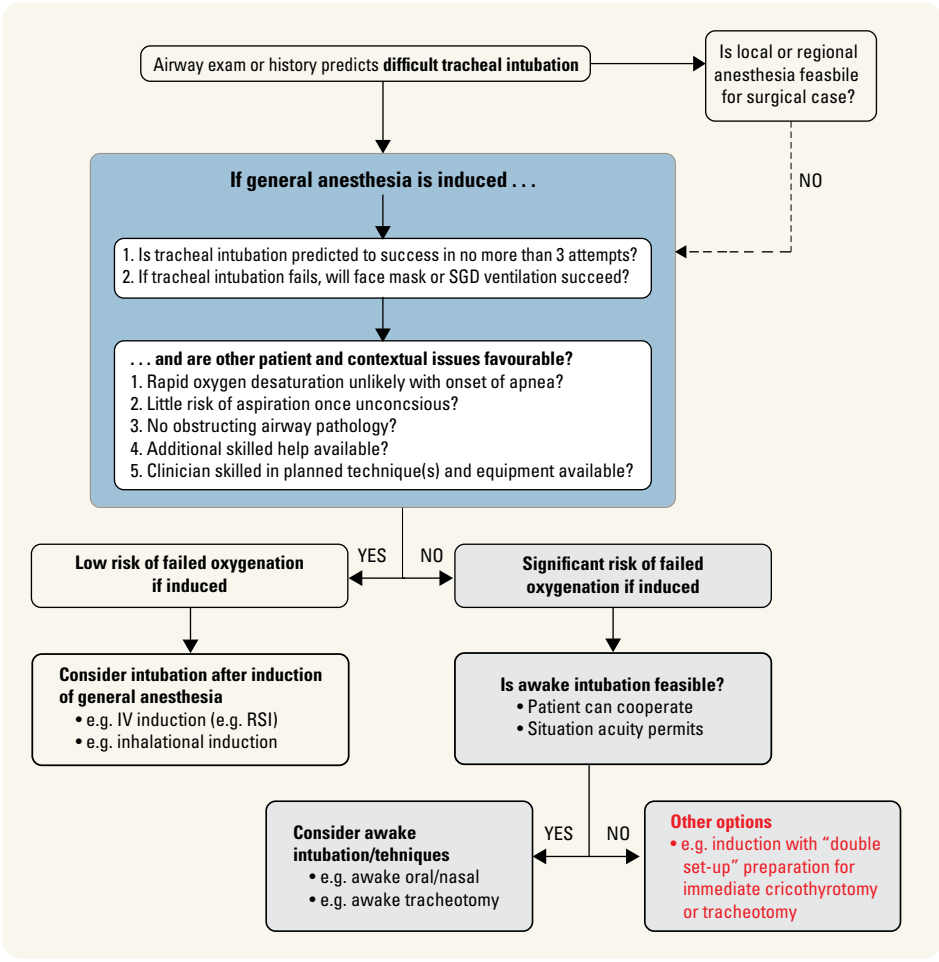



**Figure 19. Anticipated difficult tracheal intubation**
IV = intravenous; RSI = rapid sequence induction/intubation; SGD = supraglottic device

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# Advanced Cardiac Life Support Guidelines

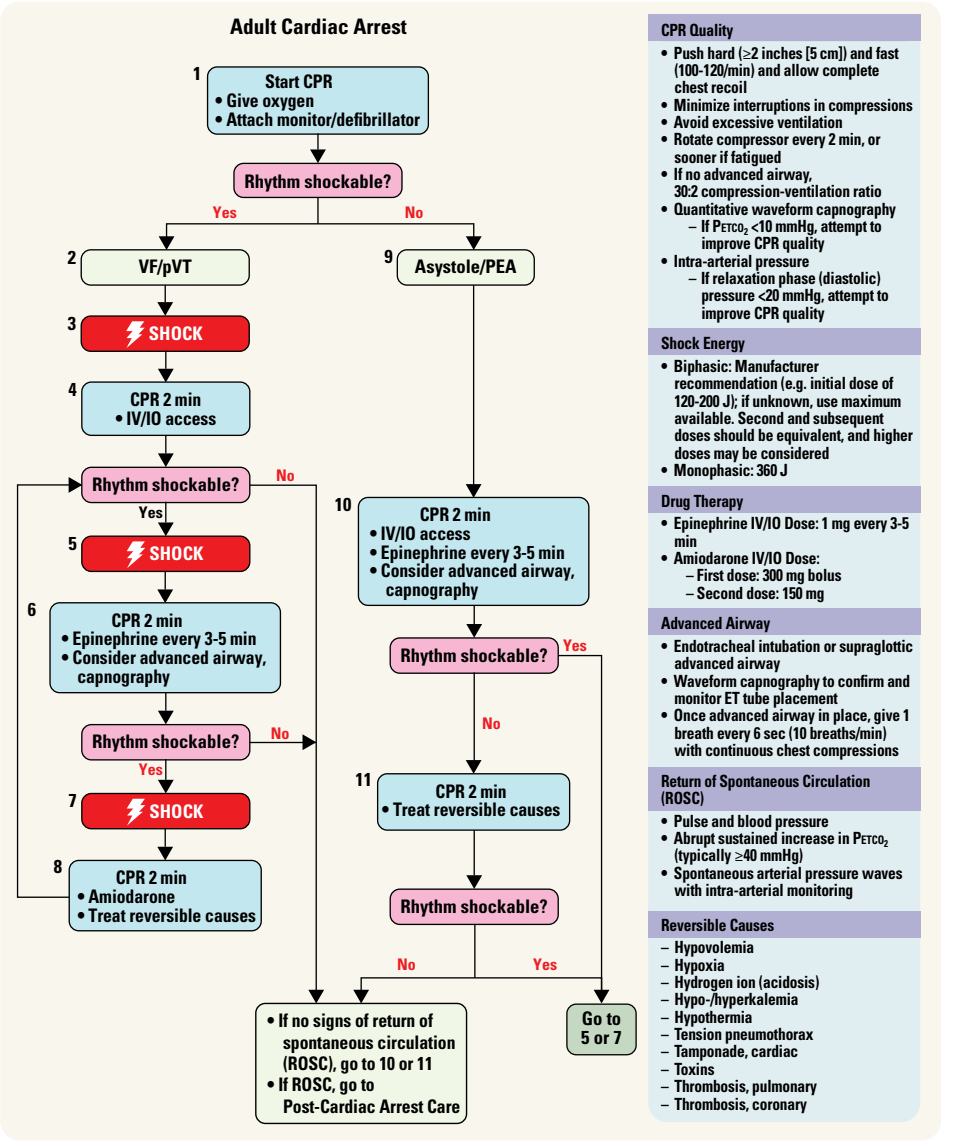



**Figure 20. Adult cardiac arrest algorithm**

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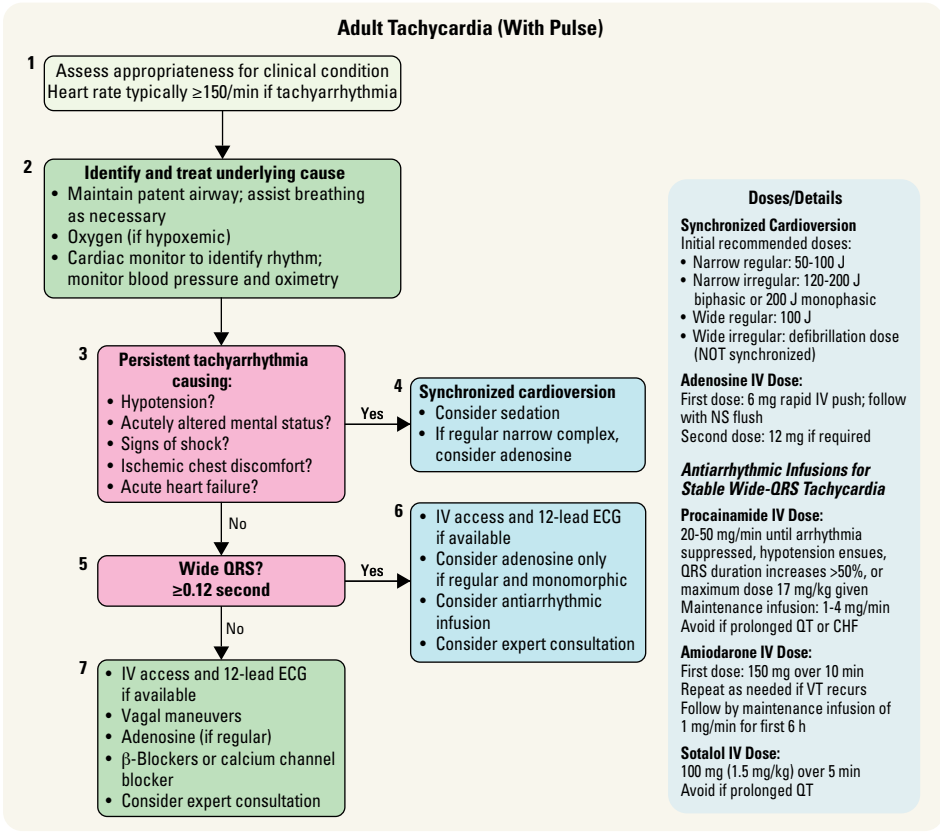



**Figure 21. Adult tachycardia algorithm**

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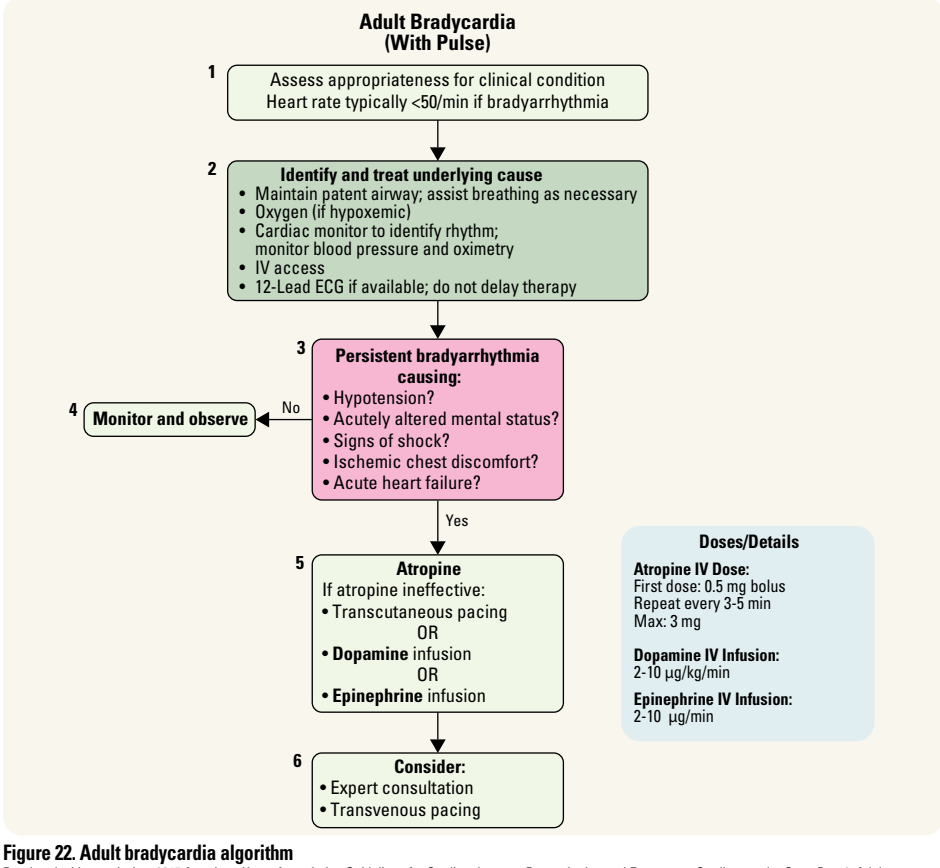



**Figure 22. Adult bradycardia algorithm**

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# C Cardiology and Cardiac Surgery

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# Acronyms

| | |
|---|---|
| A | atrium |
| AAA | abdominal aortic aneurysm |
| ACEI | angiotensin converting enzyme inhibitor |
| ACS | acute coronary syndrome |
| AFib | atrial fibrillation |
| AR | aortic regurgitation |
| ARB | angiotensin receptor blocker |
| ARDS | acute respiratory distress syndrome |
| AS | aortic stenosis |
| ASA | acetylsalicylic acid (Aspirin®) |
| ASD | atrial septal defect |
| AV | atrioventricular |
| AVNRT | atrioventricular nodal re-entrant tachycardia |
| AVRT | atrioventricular re-entrant tachycardia |
| BBB | bundle brunch block |
| BNP | brain natriuretic peptide |
| BP | blood pressure |
| BiVAD | biventricular assist device |
| CABG | coronary artery bypass graft |
| CAD | coronary artery disease |
| CCB | calcium channel blocker |
| CHD | coronary heart disease |
| CHF | congestive heart failure |
| CO | cardiac output |
| COPD | chronic obstructive pulmonary disease |
| CXR | chest x-ray |
| DCM | dilated cardiomyopathy |
| DM | diabetes mellitus |
| DOAC | direct oral anticoagulant |
| DVT | deep vein thrombosis |
| ECASA | enteric coated ASA |
| ECG | electrocardiogram |
| Echo | echocardiogram |
| EDP | end diastolic pressure |
| EPS | electrophysiology studies |
| EtOH | ethanol/alcohol |
| GERD | gastroesophageal reflux disease |
| HCM | hypertrophic cardiomyopathy |
| HFPEF | heart failure with preserved ejection fraction |
| HFREF | heart failure with reduced ejection fraction |
| HOCM | hypertrophic obstructive cardiomyopathy |
| HR | heart rate |
| HTN | hypertension |
| ICD | implantable cardioverter-defibrillator |
| IE | infective endocarditis |
| JVP | jugular venous pressure |
| LA | left atrium |
| LAE | left atrial enlargement |
| LBB | left bundle branch |
| LBBB | left bundle branch block |
| LLSB | left lower sternal border |
| LMWH | low molecular weight heparin |
| LV | left ventricle |
| LVAD | left ventricular assist device |
| LVEF | left ventricular ejection fraction |
| LVH | left ventricular hypertrophy |
| LVOT | left ventricular outflow tract |
| MAT | multifocal atrial tachycardia |
| MI | myocardial infarction |
| MPI | myocardial perfusion imaging |
| MR | mitral regurgitation |
| MS | mitral stenosis |
| NSR | normal sinus rhythm |
| NSTEMI | non-ST elevation myocardial infarction |
| OPCAB | off-pump coronary artery bypass |
| OS | opening snap |
| PAC | premature atrial contraction |
| PCI | percutaneous coronary intervention |
| PCWP | pulmonary capillary wedge pressure |
| PDA | patent ductus arteriosus |
| PE | pulmonary embolism |
| PFO | patent foramen ovale |
| PIV | posterior-interventricular artery |
| PMI | point of maximal impulse |
| PND | paroxysmal nocturnal dyspnea |
| PUD | peptic ulcer disease |
| PVC | premature ventricular contraction |
| PVD | peripheral vascular disease |
| RA | right atrium |
| RAAS | renin angiotensin aldosterone system |
| RAE | right atrial enlargement |
| RBB | right bundle branch |
| RBBB | right bundle branch block |
| RCM | restrictive cardiomyopathy |
| RV | right ventricle |
| RVAD | right ventricular assist device |
| RVH | right ventricular hypertrophy |
| SA | sinoatrial |
| SAM | systolic anterior motion |
| SCD | sudden cardiac death |
| SEM | systolic ejection murmur |
| SLE | systemic lupus erythematosus |
| SNS | sympathetic nervous system |
| SOB | shortness of breath |
| SOBOE | shortness of breath on exertion |
| STEMI | ST elevation myocardial infarction |
| SV | stroke volume |
| SVC | superior vena cava |
| SVR | systemic vascular resistance |
| SVT | supraventricular tachycardia |
| TB | tuberculosis |
| TEE | transesophageal echocardiography |
| TIA | transient ischemic attack |
| TR | tricuspid regurgitation |
| TTE | transthoracic echocardiography |
| UA | unstable angina |
| V | ventricle |
| VAD | ventricular assist device |
| VFib | ventricular fibrillation |
| VT | ventricular tachycardia |
| VTE | venous thromboembolism |
| WPW | Wolff-Parkinson-White |

# Basic Anatomy Review

## Coronary Circulation

- conventional arterial supply to the heart arises from the right and left coronary arteries, which originate from the root of the aorta
  - right coronary artery (RCA):
    - acute marginal branches
    - atrioventricular (AV) nodal artery
    - posterior descending artery (PDA) = posterior interventricular artery (PIV)
  - left main coronary artery (LCA):
    - left anterior descending artery (LAD)
      - septal branches
      - diagonal branches
    - left circumflex artery (LCx)
      - obtuse marginal branches
- dominance of circulation
  - determined by whether the RCA or the LCx supplies the PDA
    - right-dominant circulation: PDA and at least one posterolateral branch arise from RCA (80%)
    - left-dominant circulation: PDA and at least one posterolateral branch arise from LCx (15%)
    - balanced circulation: dual supply of posteroinferior LV from RCA and LCx (5%)
- the sinoatrial (SA) node is supplied by the SA nodal artery, which may arise from the RCA (60%) or LCA (40%)
- most venous blood from the heart drains into the RA through the coronary sinus, although a small amount drains through Thebesian veins into all four chambers, contributing to the physiologic R-L shunt

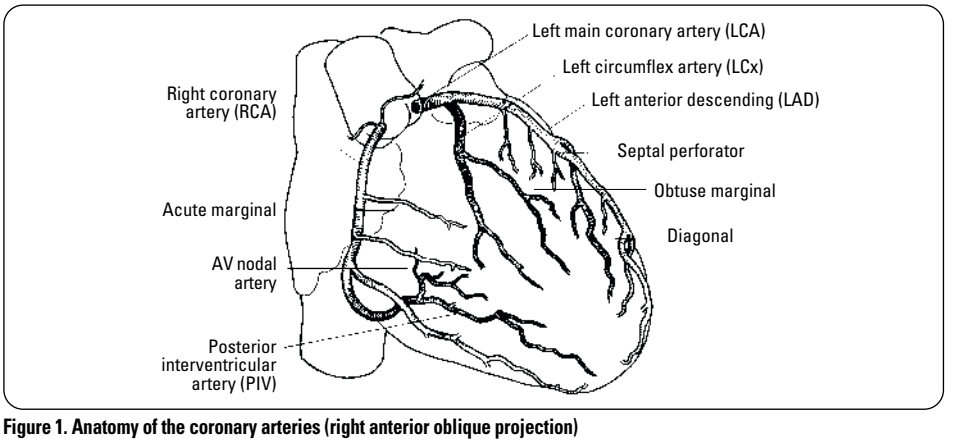



**Figure 1. Anatomy of the coronary arteries (right anterior oblique projection)**

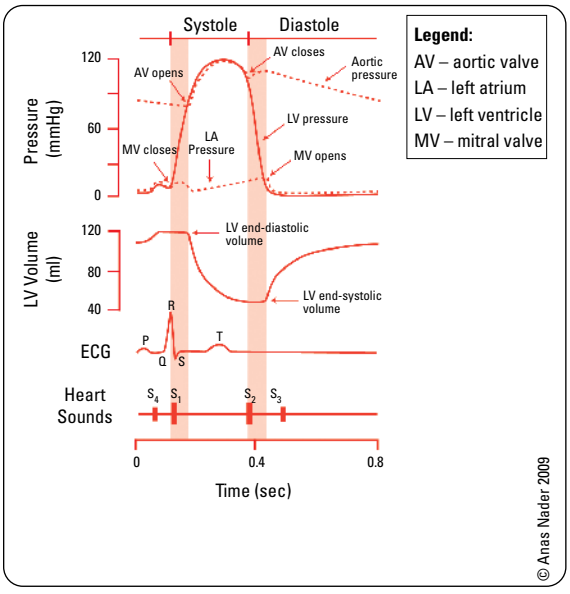



**Figure 2a. Cardiac cycle**
Grey shaded bars indicate isovolumic contraction (left) and isovolumic relaxation (right)

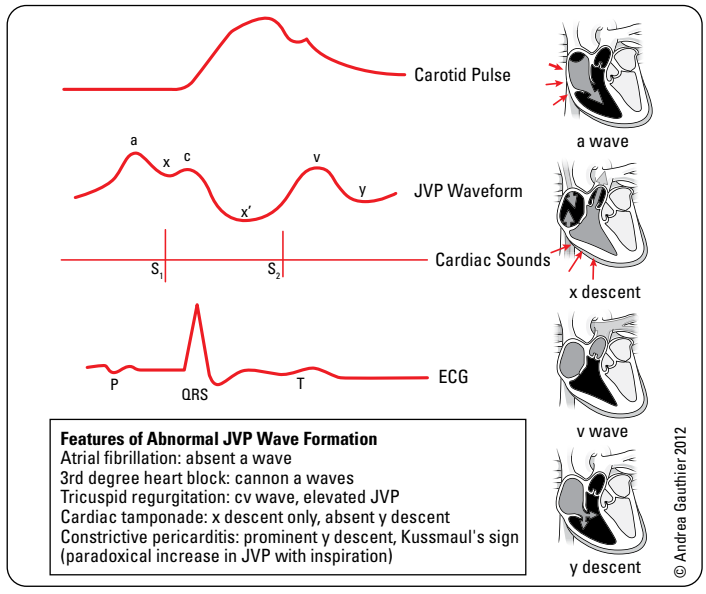



**Figure 2b. JVP waveform**

# Cardiac Anatomy

- **layers of the heart**
  - endocardium, myocardium, epicardium, visceral pericardium, pericardial cavity, parietal pericardium
- **valves**
  - semilunar valves:
    - aortic valve, 3 valve leaflets: separates LV and ascending aorta
    - pulmonic valve, 3 valve leaflets: separates RV and main pulmonary artery (PA)
  - atrioventricular valves: subvalvular apparatus present in the form of chordae tendinae and papillary muscles
    - tricuspid valve, 3 valve leaflets: separates RA and RV
    - mitral/bicuspid valve, 2 valve leaflets: separates LA and LV
- **conduction system**
  - SA node governs pacemaking control; the heart beat originates here
  - anterior-, middle-, and posterior-internal nodal tracts carry impulses in the right atrium and along Bachmann's bundle in the left atrium
  - atrial impulses converge at the AV node
  - the AV node is the only conducting tract from the atria to the ventricles because of electrical isolation by the annulus fibrosis (except when accessory pathways are present)
    - AV node connects to the bundle of His, which divides into left and right bundle branches (LBB and RBB)
  - LBB further splits into anterior and posterior fascicles
  - RBB and fascicles of LBB give off Purkinje fibres which conduct impulses into the ventricular myocardium

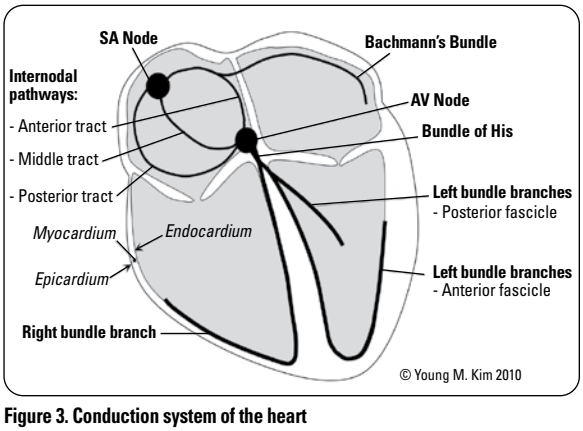



**Figure 3. Conduction system of the heart**

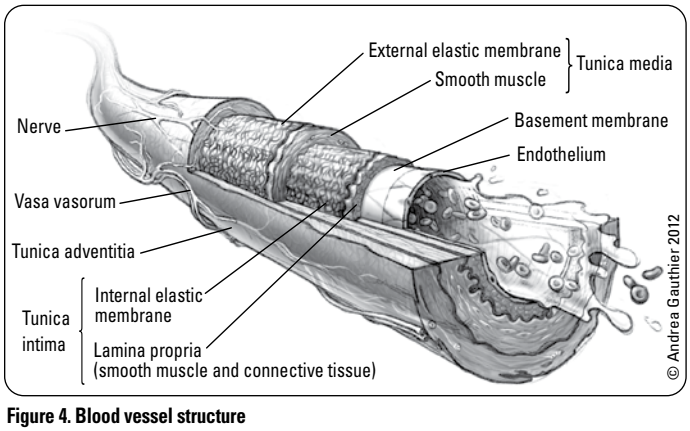



**Figure 4. Blood vessel structure**

- **cardiovascular innervation**
  - sympathetic nerves
    - innervate the SA node, AV node, ventricular myocardium, and vasculature
    - SA node (β1) increased activity leads to increased heart rate via more frequent impulse from pacemaking cells (increased chronotropy - increased HR)
    - cardiac muscle (β1) fibres increase contractility (inotropy - leads to increased SV)
    - stimulation of β1- and β2-receptors in the skeletal and coronary circulation causes vasodilatation
  - parasympathetic nerves
    - innervate the SA node, AV node, and atrial myocardium but few vascular beds
    - at rest, vagal tone dominates the tonic sympathetic stimulation of the SA node and AV node resulting in slowing of pacemaker activity (leading to a heart rate at rest slower than the intrinsic heart rate) and conduction (i.e. reduced dromotropy – if only affecting AV node conduction)
    - parasympathetics have very little impact on total peripheral vascular resistance

# Differential Diagnoses of Common Presentations

Note: **bold** text indicates most common, underlined text indicates life threatening condition

## Chest Pain

- cardiac
  - MI, angina, myocarditis, and pericarditis/Dressler's syndrome
- pulmonary
  - PE, pneumothorax/hemothorax, tension pneumothorax, pneumonia, empyema, pulmonary neoplasm, bronchiectasis, pleuritis, and TB
- gastrointestinal
  - esophageal: **GERD**, esophageal rupture, spasm, esophagitis, ulceration, achalasia, neoplasm, and Mallory-Weiss syndrome
  - other structures: PUD, gastritis, pancreatitis, and biliary colic
- mediastinal
  - lymphoma, thymoma
- vascular
  - dissecting aortic aneurysm, aortic rupture
- surface structures
- costochondritis
- rib fracture
- skin (bruising, herpes zoster)
- breast
- anxiety/psychosomatic

## Loss of Consciousness

**1. Causes of true syncope (impaired cerebral perfusion)**
- inadequate circulating volume (bleeding, hypovolemia with orthostasis)
- obstruction to blood flow
  - tamponade
  - pulmonary embolism
  - severe pulmonary hypertension
  - severe obstructive valve disease (mitral and aortic stenosis)
  - left ventricular outflow obstruction (HCM)
  - cerebrovascular events (e.g. CVA, TIA)
- sudden loss of cardiac output
  - tachyarrhythmia, ventricular tachycardia, VF
  - severe bradycardia (AV block/AV dyssynchrony)
- reflex mediated/reflex dysfunction
  - **vasovagal** (most common)
  - situational (micturition, cough, carotid hypersensitivity)
  - autonomic dysfunction (often associated with neurologic diseases)

**2. Loss of consciousness NOT due to impaired cerebral perfusion**
- seizure
- hypoglycemia
- severe hypoxia or hypercarbia
- psychiatric
- •adverse drug events (e.g. anti-hypertensives)

## Local Edema

- venous or lymphatic obstruction
  - thrombophlebitis/deep vein thrombosis, venous insufficiency, chronic lymphangitis, lymphatic tumour infiltration, filariasis
- inflammation/infection
- trauma

## Generalized Edema

- increased hydrostatic pressure/fluid overload
  - heart failure, pregnancy, drugs (e.g. CCBs), iatrogenic (e.g. IV fluids)
- decreased oncotic pressure/hypoalbuminemia
  - **liver cirrhosis**, nephrotic syndrome, malnutrition
- increased interstitial oncotic pressure
  - myxedema
- increased capillary permeability
  - severe sepsis
- hormonal
  - hypothyroidism, exogenous steroids, pregnancy, estrogens

## Palpitations

- palpitations that are continuous rapid heart action:
  - conditions causing sinus tachycardia: endocrine (thyrotoxicosis, pheochromocytoma, and hypoglycemia), systemic (anemia, fever), drugs (stimulants and anticholinergics), and psychiatric (panic attacks)
  - conditions causing pathologic tachycardia: SVT (atrial tach, A fib, and A flutter) and re-entrant SVT, VT
- palpitations with irregular/intermittent sensations e.g. PACs, PVCs

## Dyspnea

- cardiovascular
  - due to elevated pulmonary venous pressure: acute MI, CHF/LV failure, aortic/mitral stenosis, aortic/mitral regurgitation, arrhythmia, cardiac tamponade, constrictive pericarditis, and left-sided obstructive lesions (e.g. left atrial myxoma)
- respiratory
  - airway disease
    - asthma, COPD exacerbation, and upper airway obstruction (anaphylaxis, foreign body, and mucus plugging)
  - parenchymal lung disease
    - ARDS, pneumonia, interstitial lung disease
  - pulmonary vascular disease
    - PE, pulmonary HTN, pulmonary vasculitis
  - pleural disease
    - pneumothorax, pleural effusion
- neuromuscular and chest wall disorders
  - C-spine injury
    - polymyositis, myasthenia gravis, Guillain-Barré syndrome, and kyphoscoliosis
- anxiety/psychosomatic
- hematological/metabolic
  - anemia, acidosis, hypercapnia
- drugs and poisons
  - CNS depressants, carbon monoxide poisoning

# Cardiac Diagnostic Tests

## Electrocardiography Basics

### Description

- a graphical representation (time vs. amplitude of electrical vector projection) of the heart's electrical activity
- on the ECG graph
  - the horizontal axis represents time (at usual paper speed 25 mm/s)
    - 1 mm (1 small square) = 40 msec
    - 5 mm (1 large square) = 200 msec
  - the vertical axis represents voltage (at usual standard gain setting 10 mm/mV)
    - 1 mm (1 small square) = 0.1 mV
    - 10 mm (2 large squares) = 1 mV

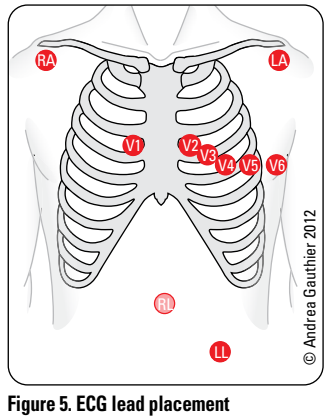



**Figure 5. ECG lead placement**

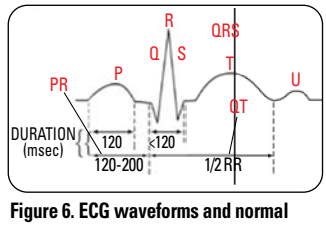



**Figure 6. ECG waveforms and normal values**

- leads
  - standard 12-lead ECG
  - limb (bipolar) leads: I, II, III, aVL, aVR, aVF
  - precordial (unipolar) leads: V1-V6 (V1-V2 septal, V3-V4 anterior, V5-V6 lateral)
- additional leads
  - right-sided leads: V3R-V6R (useful in RV infarction and dextrocardia)
- leads that indicate specific regions of the heart:
  - lateral wall = I, aVL, V5, V6
  - inferior wall = II, III, aVF
  - anterior wall= V1-V4

### Indications for brief (12-lead ECG) or prolonged (24 hrs or more) monitoring

- detect myocardial injury, ischemia, and the presence of prior infarction
- conditions associated with palpitations or risk of serious arrhythmias (e.g. WPW, long QT, HCM, heart block, and bradycardia)
- recording of cardiac rhythm during symptoms or antiarrhythmic drug monitoring
- conduction abnormalities (e.g. LBBB/RBBB)
- electrolytes abnormalities (e.g. hyperkalemia/hypokalemia)
- assessment of cardiac structure and function. (e.g. RVH/LVH and cardiomyopathy)
- non-sustained arrhythmias that can lead to prophylactic intervention

**Rate Calculations**
- Examples, practice

For more examples and practice visit www.ecgmadesimple.com

# Approach to ECGs

### Introduction

Below, we are presenting both the Classical Approach and the newer PQRSTU Approach to provide students with different ways to view the ECG. Despite methodological differences, the rigor and final result is the same.

## Classical Approach to ECGs

**Classical Approach to ECG**
- Rate
- Regular rhythm (defined by equal R-R or P-P intervals between beats)
- Axis
- Conduction abnormalities
- Hypertrophy/chamber enlargement
- Ischemia/infarction
- Miscellaneous ECG changes

### RATE

- normal = 60-100 bpm (atrial rate: 150-250 bpm = paroxysmal tachycardia, 250-350 bpm = atrial flutter, >350 bpm = AFib, in AF atrial "rate" not discernible )
- regular rhythm (defined by equal R-R or P-P intervals between beats)
  - to calculate the rate, divide 300 by number of large squares between 2 QRS complexes (there are 300 large squares in 1 min: 300 x 200 msec = 60 sec)
  - or use the square counting method by counting the number of big boxes between the R waves using the following numbers: 300-150-100-75-60-50
- irregular rhythm
  - rate = 6 x number of R-R intervals in 10 s (the "rhythm strips" are 10 sec recordings)
- atrial escape rhythm in case of sinus node failure = 60-80 bpm; junctional escape rhythm = 40-60 bpm; ventricular escape rhythm = 20-40 bpm

**Differential Diagnosis for Left Axis Deviation (LAD)**
- Left anterior hemiblock
- Inferior MI
- WPW
- RV pacing
- Normal variant
- Elevated diaphragm
- Lead misplacement
- Endocardial cushion defect

### RHYTHM

- regular: R-R interval is the same across the tracing
- irregular: R-R interval varies across the tracing
- regularly irregular: repeating pattern of varying R-R intervals e.g. Atrial flutter with variable block
- irregularly irregular: R-R intervals vary erratically e.g. AFib, VFib
- normal sinus rhythm (NSR)
  - P wave precedes each QRS; QRS follows each P wave
  - P wave axis is normal (positive in 2 out of the 3 following leads I, II, aVF)
  - rate between 60-100 bpm

**Differential Diagnosis for Right Axis Deviation (RAD)**
- RVH
- Left posterior hemiblock
- Pulmonary embolism
- COPD
- Lateral MI
- WPW
- Dextrocardia
- Septal defects

### AXIS

- mean axis indicates the direction of the mean vector
- can be determined for any waveform (P, QRS, T)
- the standard ECG reported QRS axis usually refers to the mean axis of the frontal plane – it indicates the mean direction of ventricular depolarization forces
- QRS axis in the frontal plane
  - normal axis: -30° to 90° (i.e. positive QRS in leads I and II)
  - left axis deviation (LAD): axis <-30°
  - right axis deviation (RAD): axis >90°
- QRS axis in the horizontal plane is not routinely calculated
  - transition from negative to positive is usually in lead V3

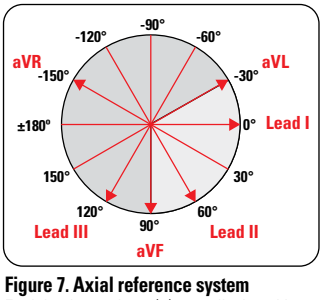



**Figure 7. Axial reference system**
Each lead contains a (+) area displayed by the bold arrows. Impulses traveling toward the positive region of the lead results in an upward deflection in that lead. Normal QRS axis is between -30° and +90°

### Table 1. Conduction Abnormalities

| Left Bundle Branch Block (LBBB) | Right Bundle Branch Block (RBBB) |
|---|---|
| **Complete LBBB**<br>QRS duration >120 msec<br>Broad notched R waves in leads V4, and V5, and/or I, aVL<br>Deep broad S waves in leads V1-2<br>Secondary ST-T changes (-ve in leads with broad notched R waves, +ve in V1-2) are usually present<br>LBBB can mask ECG signs of MI<br>LBBB: lead V 1 negative, V6 positive and notched | **Complete RBBB**<br>QRS duration >120 msec<br>Positive QRS in lead V1 (rSR' or occasionally broad R wave)<br>Broad S waves in leads I, V5-6 (>40 msec)<br>Usually secondary T wave inversion in leads V1-2<br>Frontal axis determination using only the first 60 msec<br>RBBB: V1 is positive (rSR'), V6 has broad S wave |

| Left Anterior Fascicular Block (LAFB) (Left Anterior Hemiblock) | Left Posterior Fascicular Block (LPFB) (Left Posterior Hemiblock) | Bifascicular Block |
|---|---|---|
| **Left Axis Deviation (-30° to -90°)**<br>Small q and prominent R in leads I and aVL<br>Small r and prominent S in leads II, III, and aVF | **Right Axis Deviation (110° to 180°)**<br>Small r and prominent S in leads I and aVL<br>Small q and prominent R in leads II, III, and aVF | **RBBB Pattern**<br>Small q and prominent R<br>The first 60 msec (1.5 small squares) of the QRS shows the pattern of LAFB or LPFB<br>Bifascicular block refers to impaired conduction in two of the three fascicles, most commonly a RBBB and left anterior hemiblock; the appearance on an ECG meets the criteria for both types of blocks |

### Nonspecific Intraventricular Block

- QRS duration >120 msec
- absence of definitive criteria for LBBB or RBBB

### Table 2. Hypertrophy/Chamber Enlargement

| Left Ventricular Hypertrophy (LVH) | Right Ventricular Hypertrophy (RVH) |
|---|---|
| S in V1 + R in V5 or V6 >35 mm above age 40, (>40 mm for age 31-40, >45 mm for age 21-30)<br>R in aVL >11 mm<br>R in I + S in III >25 mm<br>Additional criteria<br>LV strain pattern (asymmetric ST depression and T wave inversion in leads I, aVL, V4-V6)<br>Left atrial enlargement<br>N.B. The more criteria present, the more likely LVH is present. If only one voltage criteria present, it is called minimal voltage criteria for LVH which could be a normal variant | Right axis deviation<br>R/S ratio >1 or qR in lead V1<br>RV strain pattern: ST segment depression and T wave inversion in leads V1-2 |
| **Left Atrial Enlargement (LAE)** | **Right Atrial Enlargement (RAE)** |
| Biphasic P wave with the negative terminal component of the P wave in lead V1 ≥1 mm wide and ≥1 mm deep<br>P wave >100 msec, could be notched in lead II ("P mitrale") | P wave >2.5 mm in height in leads II, III, or aVF ("P pulmonale") |

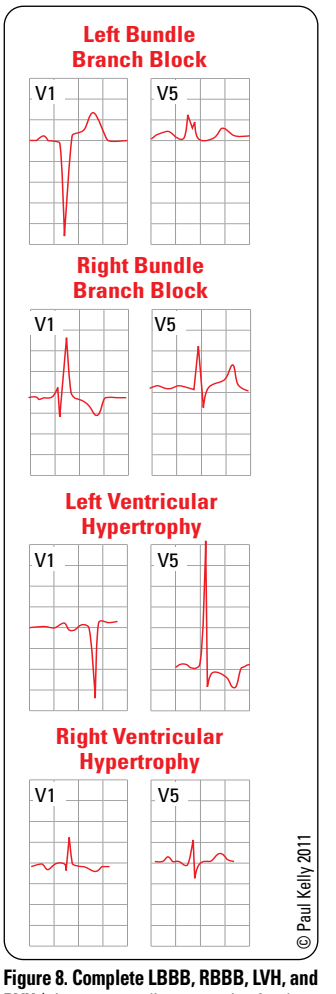



**Figure 8. Complete LBBB, RBBB, LVH, and RVH** (please see online examples for the full range of waveforms and the text for additional characteristics)

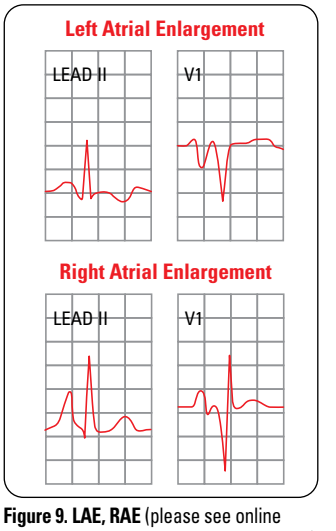



**Figure 9. LAE, RAE** (please see online examples and the text for characteristics)

## ISCHEMIA/INFARCTION

- look for the anatomic distribution of the following ECG abnormalities (see Table 3)
  - ischemia
    - ST segment depression
    - T wave inversion (most commonly in V1-V6)
  - injury/infarct
    - transmural (involving the epicardium)
    - ST elevation in the leads facing the area injured/infarcted
    - subendocardial
    - marked ST depression in the leads facing the affected area
    - may be accompanied by enzyme changes and other signs of MI

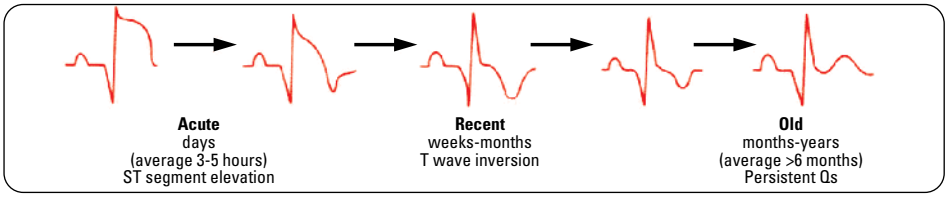



**Figure 10. Typical ECG changes with infarction**

  - ST elevation
    - new ST elevation in two contiguous leads of >0.1 mV in all leads other than leads V2-V3
    - for leads V2-V3: ≥0.2 mV in men ≥40 yr, ≥0.25 mV in men <40 yr, or ≥0.15 mV in women

- "typical" sequential changes of evolving MI
  1. hyperacute T waves (tall, symmetric T waves) in the leads facing the infarcted area, with or without ST elevation
  2. ST elevation (injury pattern) in the leads facing the infarcted area
     - usually in the first hours post infarct
     - in acute posterior MI, there is ST depression in V1-V3 (reciprocal to ST elevation in the posterior leads that are not recorded in the standard 12-lead ECG) hence get a 15-lead ECG
  3. significant Q waves: >40 msec or >1/3 of the total QRS amplitude and present in at least 2 consecutive leads in the same territory (hours to days post-infarct)
     - Q waves of infarction may appear in the very early stages, with or without ST changes
     - non-Q wave infarction: there may be only ST or T changes despite clinical evidence of infarction
  4. inverted T waves (one day to weeks after infarction)
- completed infarction
  - abnormal Q waves (Q waves may be present in lead III in normal individuals due to initial septal depolarization)
  - duration >40 msec (>30 msec in aVF for inferior infarction)
  - Q wave is >1/3 of the total QRS amplitude
  - present in at least 2 consecutive leads in the same territory
  - abnormal R waves (R/S ratio >1, duration >40 msec) in V1 and occasionally in V2 are found in posterior infarction (usually in association with signs of inferior and/or lateral infarction)

**Table 3. Areas of Infarction/Ischemia (right dominant anatomy)**

| Vessel Usually Involved | Infarct Area (LAD and LC) | Leads (LAD and LC) |
|---|---|---|
| **Left Anterior Descending (LAD)** | Anteroseptal<br>Anterior<br>Anterolateral<br>Extensive anterior | V1, V2<br>V3, V4<br>I, aVL, V3-6<br>I, aVL, V1-6 |
| **Right Coronary Artery (RCA)** | Inferior<br>Right ventricle<br>Posterior MI (assoc. with inf. MI) | II, III, aVF<br>V3R, V4R (right sided chest leads)<br>V1, V2 (prominent R waves) |
| **Left Circumflex (LCX)** | Lateral<br>Isolated posterior MI | I, aVL, V5-6<br>V1, V2 (prominent R waves) |

## MISCELLANEOUS ECG CHANGES

### Electrolyte Disturbances

- hyperkalemia
  - mild to moderate ($K^+$ 5-7 mmol/L): tall, peaked T waves
  - severe ($K^+$ >7 mmol/L): progressive changes whereby P waves flatten and disappear, QRS widens and may show abnormal morphology, axis shifts left or right, ST shift with tall T waves, eventually becomes a "sine wave" pattern
- hypokalemia
  - ST segment depression, prolonged QT interval (with risk for Torsades de Pointes ventricular tachycardia if extreme), low T waves, prominent U waves (U>T)
  - enhances the toxic effects of digitalis
- hypercalcemia
  - shortened QT interval (more extracellular $Ca^{2+}$ means shorter plateau in cardiac action potential)
- hypocalcemia
  - prolonged QT interval (less extracellular $Ca^{2+}$ means longer plateau in cardiac action potential)

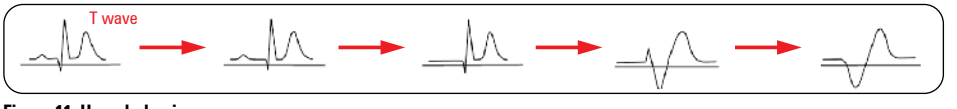



**Figure 11. Hyperkalemia**

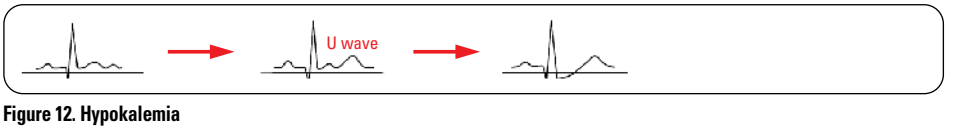



**Figure 12. Hypokalemia**

### Hypothermia

- sinus bradycardia
- when severe, prolonged QRS and QT intervals
- AFib with slow ventricular response and other atrial/ventricular dysrhythmias
- Osborne J waves: "hump-like" waves at the junction of the J point and the ST segment

### Pericarditis

- early: diffuse ST segment elevation ± PR segment depression, upright T waves
- later: isoelectric ST segment, flat or inverted T waves
- ± tachycardia

**Pacemakers**

- Demand pacemaker has discharge (narrow vertical spike on ECG strip) prior to widened QRS
- Atrial pacemaker has discharge prior to P wave
- Triggered pacemaker has discharge following the P wave but prior to the widened QRS
- Atrial and ventricular pacing have discharge before the P wave and widened QRS wave

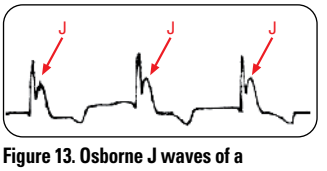



**Figure 13. Osborne J waves of a hypothermic patient**

### Drug Effects

- digitalis – rare in 2018; <1/1000 cardiac patients overall
  - therapeutic levels may be associated with "digitalis effect"
    - ST downsloping or "scooping"
    - T wave depression or inversion
    - QT shortening ± U waves
    - slowing of ventricular rate in AFib
    - toxic levels associated with:
      - arrhythmias: paroxysmal atrial tachycardia (PAT) with conduction block, severe bradycardia in AFib, accelerated junctional rhythms, PVCs, ventricular tachycardia (see *Arrhythmias*, C16)
      - "regularization" of ventricular rate in AFib due to a junctional rhythm and AV dissociation
- amiodarone, quinidine, phenothiazines, tricyclic antidepressants, antipsychotics, some antihistamines, and some antibiotics (prolonged QT interval, U waves)

**Digitalis Side Effects**
Palpitations, fatigue, visual changes (yellow vision), decreased appetite, hallucinations, confusion, and depression

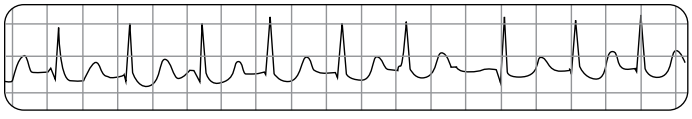


**Figure 14. Atrial fibrillation, ST change due to digitalis ("digitalis effect")**

### Pulmonary Disorders

- cor pulmonale (often secondary to COPD)
  - low voltage, right axis deviation (RAD), poor R wave progression in precordial leads
  - RAE and RVH with strain
  - multifocal atrial tachycardia (MAT)
- massive pulmonary embolism (PE)
  - sinus tachycardia and AFib/atrial flutter are the most common arrhythmias
  - RAD, RVH with strain
  - most specific sign is S1Q3T3 (S in I, Q and inverted T wave in III) but rather uncommon

## Alternative PQRSTU Approach to ECGs

Note: the PQRSTU Approach is organized a different way based on the anatomy of the ECG

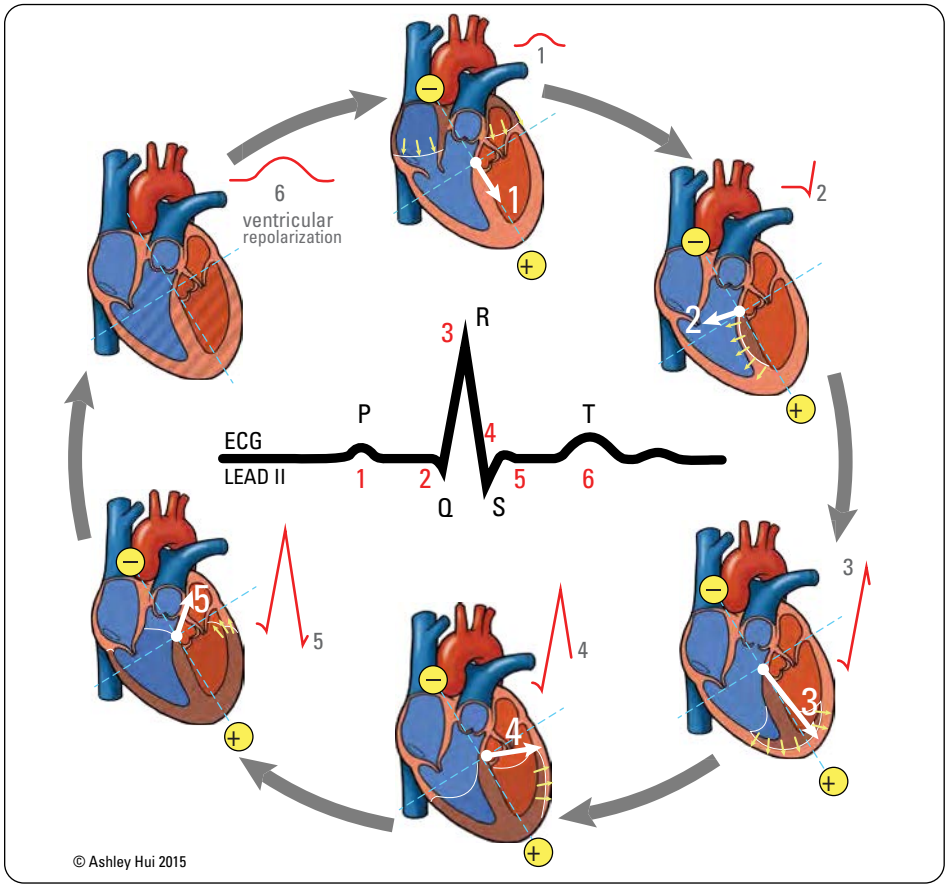



**Figure 15. ECG correlations with heart activity**

**PQRSTU approach to ECGs**
**P** wave
**P-R** interval
**QRS** complex
**ST** segment
**T** wave
**Q-T** interval
**U** wave

## P WAVE
- the P wave represents atrial contraction; best seen in leads: II and V1
  - lead II: the P wave should be rounded, <120 msec and <2.5 mm in height
  - lead V1: the P wave is biphasic with a positive phase slightly greater than the negative phase
- atrial flutter: sawtooth P wave with continuous atrial activity at 300/min indicates the interval (Hint: flip the ECG upside-down to see it better if unclear)
- atrial fibrillation: absent P wave, may have fibrillatory wave, irregular rhythm
- right atrial enlargement: tall P wave (>2.5 mm) in II or V1 (P pulmonale)
- left atrial enlargement: biphasic P wave with negative deflection >1 mm deep or >1 mm wide in V1, wide (>100 msec) notched P wave in II may be present (P mitrale)

## P-R INTERVAL
- the P-R interval indicates the interval between sinus node activation and the start of ventricular depolarization
  - includes the impulse traveling through the atrium, the AV node, and the bundle of the magnitude of the conduction velocity is referred to as "dromotropy" ( faster = positive, slower = negative dromotropy)
  - positive dromotropy associated with increased conduction velocity (e.g. sympathetic stimulation), while negative dromotropy with decreased velocity (e.g. vagal stimulation)
- P-R interval should be 120-200 msec
- long P-R interval (>200 msec)
  - heart block
    - first degree: fixed, prolonged P-R interval (though every P wave has a QRS following)
    - second and third degree AV block: some P waves are NOT followed by a QRS
    - second degree Mobitz I (Wenckebach): gradual prolongation of the P-R interval precedes a dropped P wave
    - second degree Mobitz II (Hay): fixed P-R interval with ratio of beat to dropped beat (e.g. for every 3 beats, there is one dropped beat [3:1])
  - third degree/complete: constant P-P and R-R intervals but variable P-R intervals
  - sinus bradycardia (normal to have long P-R if heart rate slow)
  - hypokalemia
  - "trifascicular" block -1st degree AV block with LAHF and complete RBBB
- short P-R interval (<120 msec)
  - pre-excitation syndrome (delta wave: upswooping of P-R segment into QRS complex) due to accessory pathways
  - low atrial rhythm, P waves inverted in II, III, aVF

**Significant ECG Changes**
- Look for ST changes starting at 60 msec from J point
- J point = the junction between the QRS complex and the ST segment
- ST elevation: at least 1 mm in 2 adjacent limb leads, or at least 1-2 mm in adjacent precordial leads
- ST depression: downsloping or horizontal
- Q Wave: pathological if Q wave ≥1 small square (≥40 msec) or >33% of the total QRS

## QRS COMPLEX
- represents ventricular contraction
- rate: check if R-R interval matches the P-P interval
- amplitude: check for hypertrophy (see Table 2)
- narrow QRS (<120 msec) means that the His-Purkinje system is being used
- wide QRS (>120 msec) means that the His-Purkinje system is being bypassed or is diseased
  - BBB, VT, ventricular hypertrophy, cardiomyopathy, WPW, ectopic ventricular beat, hyperkalemia, or drugs (e.g. TCAs, antiarrhythmics)
- Q wave: the first downward deflection of the QRS complex
  - significant Q wave (>40 msec or >1/3 of total QRS amplitude) indicates myocardial necrosis (new or old)
- R and S wave abnormalities typically show pathology in terms of BBB or intraventricular abnormalities

**Insignificant Q Wave**
- Septal depolarization by the left bundle
- Seen in leads I, II, III, aVL, V5, V6
- <40 msec
- Q wave <1/3 of the total QRS amplitude

## ST SEGMENT
- located between QRS complex and the beginning of T wave
  - corresponds to the completion of ventricular depolarization
- normally at the same level as baseline (T-P segment)
- ST elevation: please see the infarct section above
- ST depression: ischemia
  - ischemia which causes ST depression can result in myocardial damage (NSTEMI)
  - lateral ST depression (leads I, aVL, V5, V6) may actually indicate a STEMI in the right heart
  - ST depression may be nonspecific, or associated with remote myocardial infarction or ischemia

## T WAVE
- repolarization phase of ventricles (repolarization of the atria is obscured by the QRS complex)
- typically positive (except in aVR and V1) on ECG but normal isolated negative T waves may be present (especially in V1 and V2)
- pathology when T wave variation occur in consecutive leads
  - inversion: BBB, ischemia, hypertrophy, drugs (e.g. digitalis), pulmonary embolism (lead III as part of S1Q3T3 sign)
  - elevation: infarction (STEMI, Prinzmetal, hyperacute), hyperkalemia (wider, peaked)
  - flattened: hypokalemia, pericarditis, drugs (e.g. digitalis), pericardial effusion
    - T waves may be flat as a nonspecific finding without clinical significance (common)
  - variations: T wave alterans; beat-to-beat variations due to PVC overlap (R on T phenomenon which may precipitate VT or VFib)
- appropriate T wave discordance: in BBB, T wave deflection should be opposite to that of the terminal QRS deflection (i.e. T wave negative if ends with R or R'; positive if ends with S)
  - inappropriate T wave concordance suggests ischemia or infarction

### Q-T INTERVAL

- duration of ventricular depolarization plus repolarization; often difficult to interpret
- corrected QT (QTc) corrects for the repolarization duration (since QT interval normally shortens with increased heart rate)
  - QTc = QT ÷ √RR (Bazett's formula)
- normal QTc is 360-450 msec for males and 360-460 msec for females
  - increased (>450 msec for males and >460 msec for females): risk of Torsades de Pointes (lethal tachyarrhythmia; rare if <520 msec)
    - genetic Long QT Syndrome (often a channelopathy)
    - drugs: antiarrhythmics (class I and III), antipsychotics (haloperidol, ziprasidone), antidepressants (citalopram), antibiotics (erythromycin, azithromycin)
    - electrolytes: low $Ca^{2+}$, low $K^{+}$, low $Mg^{2+}$
    - others: hypothyroidism, hypothermia, cardiomyopathy
  - decreased (<360 msec): risk of VFib (very rare)
    - electrolytes: high $Ca^{++}$
    - drugs: digoxin
    - others: hyperthyroidism

### U WAVE

- origin unclear but may be repolarization of Purkinje fibres or delayed/prolonged repolarization of the myocardium
- more visible at slower heart rates
- deflection follows T wave with <25% of the amplitude
- variations from norm could indicate pathologic conditions
  - prominent (>25% of T wave): electrolyte (low $K^{+}$), drugs (digoxin, antiarrhythmics)
  - inverted (from T wave): ischemia, volume overload

**Differential Diagnosis of ST Segment Changes**

**ST Elevation I HELP A PAL**
**I**schemia with reciprocal changes
**H**ypothermia (Osborne waves)
**E**arly repolarization (normal variant, need old **EC**Gs to confirm)
**L**BBB
**P**ost-MI
**A**cute STEMI
**P**rinzmetal's (Vasospastic) angina
**A**cute pericarditis (diffuse changes)
**L**eft/right ventricular aneurysm

**ST Depression WAR SHIP**
**W**PW syndrome
**A**cute NSTEMI
**R**BBB/LBBB
**S**TEMI with reciprocal changes
**H**ypertrophy (LVH or RVH) with strain
**I**schemia
**P**ost-MI

## Cardiac Biomarkers

- provide diagnostic and prognostic information in acute coronary syndromes and in heart failure

**Table 4. Cardiac Enzymes**

| Enzyme | Peak | Duration Elevated | DDx of Elevation |
|---|---|---|---|
| Troponin I, Troponin T | 1-2 d | Up to 2 wk | MI, CHF, AFib, acute PE, myocarditis, chronic renal insufficiency, sepsis, hypovolemia |
| CK-MB | 1 d | 3 d | MI, myocarditis, pericarditis, muscular dystrophy, cardiac defibrillation, chronic renal insufficiency |

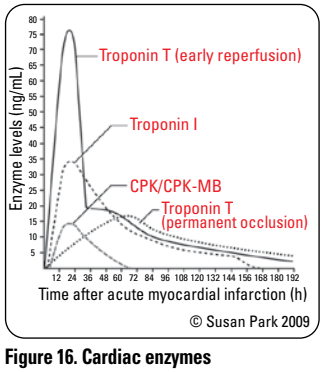



**Figure 16. Cardiac enzymes**

- check troponin I at presentation and 8 h later ± creatine kinase-MB (CK-MB; depends on local laboratory protocol)
- new CK-MB elevation can be used to diagnose re-infarction
- other biomarkers of cardiac disease
  - AST and LDH also increased in MI (low specificity)
  - BNP and NT-proBNP: secreted by ventricles in response to increased end-diastolic pressure and volume
    - DDx of elevated BNP: CHF, AFib, PE, COPD exacerbation, pulmonary HTN

**Use of B-Type Natriuretic Peptide in the Evaluation and Management of Acute Dyspnea (BASEL)**
NEJM 2004;350;647-54
**Study:** Prospective, RCT.
**Population:** 452 patients (mean age 71 yr, 58% male) with acute dyspnea; patients with severe renal disease or cardiogenic shock were excluded.
**Intervention:** Assessment including measurement of B-type natriuretic peptide or standard assessment.
**Outcome:** Time to discharge and total cost of treatment.
**Results:** Median time to discharge was significantly shorter in the intervention group when compared with the control group (8.0 vs. 11.0 d, p=0.001). Total cost was also significantly lower in the intervention group ($5410 vs. $7264, p=0.006). In addition, the measurement of B-type natriuretic peptide significantly reduced the need for admission to hospital and intensive care. The 30-d mortality rates were similar (10% vs. 12%, p=0.45).
**Conclusions:** In patients with acute dyspnea, measurement of B-type natriuretic peptide improves clinical outcomes (need for hospitalization or intensive care) and reduces time to discharge and total cost of treatment.

## Ambulatory ECG

- **description**
  - extended ambulatory ECG monitoring
  - provides a view of only two or three leads of electrocardiographic data over an extended period of time
  - permits evaluation of changing dynamic cardiac electrical phenomena that are often transient
  - **continuous ambulatory monitor**: a small, lightweight, battery operated recorder (box or patch) that records two or three channels of electrocardiographic data
    - patient activated event markers
    - minimum of 24-72 h, up to 14 d
  - **implantable device**: subcutaneous monitoring device for the detection of cardiac arrhythmias
    - typically implanted in the left pectoral region and stores events when the device is activated automatically according to programmed criteria or manually with magnet application
    - generally used for months to years of continuous monitoring for infrequent events
- **indications**
  - evaluation of cardiac rhythm abnormalities, especially as they correlate with symptoms
  - has also been used for assessing pacemaker and implantable cardioverter-defibrillator function, evidence of myocardial ischemia, late potentials, and heart rate variability

# Echocardiography

### Transthoracic Echocardiography (TTE)

- **description**
  - ultrasound beams are directed across the chest wall to obtain images of the heart
- **indications**
  - evaluation of chamber size, LVEF, wall motion abnormalities, myocardial ischemia and complications of MI
  - evaluation of wall thickness, valve morphology, proximal great vessel morphology, pericardial effusion
  - evaluation of unexplained hypotension, murmurs, syncope, and congenital heart disease or other cardiac symptoms and unexplained signs on physical exam (i.e. leg edema)

### Transoesophageal Echocardiography (TEE)

- **description**
  - invasive procedure used to complement TTE
  - ultrasound probe inserted into the esophagus to allow for better resolution of the heart and structures
  - better visualization of posterior structures, including left atrium, mitral, and aortic valves, inter-atrial septum
- **indications**
  - should be performed as the initial test in certain life-threatening situations (e.g. aortic dissection) when other tests contraindicated (e.g. CT angiography in patient with renal failure)
  - most importantly, TTE is used to evaluate valvular morphology and function (particularly the aortic and mitral valves)
  - intracardiac thrombi, tumours, valvular vegetations (infective endocarditis), aortic dissection, aortic atheromas, prosthetic valve function, shunt, technically inadequate transthoracic study
  - evaluation for left atrialthrombus/left atrial appendage thrombus in a patient with atrial fibrillation/atrial flutter to facilitate clinical decision making regarding electrical cardioversion or ablation
- **risks**
  - serious complications are extremely rare (<1 in 5000)
  - esophageal perforation
  - gastrointestinal bleeding
  - pharyngeal hematoma

### Stress Echocardiography (SE)

- **description**
  - echocardiography using exercise (treadmill or bicycle) or pharmacologic agents (dobutamine or adenosine) as physiologic stressor
- **indications**
  - useful alternative to other stress imaging modalities
  - when ECG cannot be interpreted appropriately
  - intermediate pre-test probability with normal/equivocal exercise ECG
  - post-ACS when used to decide on potential efficacy of revascularization
  - to evaluate the clinical significance of valvular heart disease
  - evaluation of myocardial viability, dyspnea of possible cardiac origin, mitral valve disease, aortic stenosis, mitral regurgitation, pulmonary hypertension, and patients with hypertrophic cardiomyopathy (for LVOT obstruction)
  - dobutamine
    - pharmacologic stress for patients physically unable to exercise; same indications as exercise stress echo
    - low dose dobutamine stress echo can be used to assess myocardial viability and for assessing aortic stenosis with LV systolic dysfunction
- **contraindications**
  - contraindications to exercise testing (see below)
  - contraindications to dobutamine stress echocardiography: tachyarrhythmias and systemic hypertension
  - AAA has been considered as a relative contraindication to exercise testing or dobutamine stress echocardiography

### Contrast Echocardiography with Agitated Saline Contrast

- **description**
  - improves visualization and provides real-time assessment of intracardiac blood flow
  - conventional agent is agitated saline (contains microbubbles of air)
  - visualization of right heart and intracardiac shunts, most commonly patent foramen ovale (PFO) and intrapulmonary shunt

### Contrast Echocardiography with Transpulmonary Contrast Agents

- **description**
  - newer contrast agents are capable of crossing the pulmonary bed and achieving left heart opacification following intravenous injection; these contrast agents improve visualization of endocardial borders and enhance evaluation of LV ejection fraction and wall motion abnormalities (in patients with technically inadequate echocardiograms) and intracardiac mass (e.g. LV thrombus)
- **risks**
  - risk of non-fatal MI and death are rare
  - ultrasound contrast agents may cause back pain, headache, urticaria, and anaphylaxis
  - should not be done in patients with significant intra-cardiac shunts

# Stress Testing

## EXERCISE TESTING

- **description**
  - cardiovascular stress test that uses treadmill or bicycle exercise with electrocardiographic and blood pressure monitoring
- **indications**
  - patients with intermediate (10-90%) pretest probability of CAD based on age, gender, and symptoms
  - ST depression <1 mm at rest, no left bundle branch block, no digoxin or estrogen use
  - exercise test results stratify patients into 3 risk groups
    1. low risk patients can be treated medically without invasive testing
    2. intermediate risk patients may need additional testing in the form of exercise imaging studies or cardiac catheterization
    3. high risk patients should be referred for cardiac catheterization
- **contraindications**
  - acute myocardial infarction (within 2 d) or unstable angina pectoris
  - uncontrolled arrhythmias causing symptoms of hemodynamic compromise
  - symptomatic severe valvular stenosis
  - uncontrolled symptomatic heart failure
  - active endocarditis or acute myocarditis or pericarditis
  - acute aortic dissection
  - acute pulmonary or systemic embolism
  - acute non-cardiac disorders that may affect exercise performance or may be aggravated by exercise
  - termination of exercise testing
    - patient's desire to stop
    - drop in systolic blood pressure of >10 mmHg from baseline despite an increase in workload, when accompanied by other evidence of ischemia
    - moderate to severe angina
    - ST elevation (>1 mm) in leads without diagnostic Q-waves (other than V1 or aVR)
    - increasing nervous system symptoms (e.g. ataxia, dizziness, or near syncope)
    - signs of poor perfusion (cyanosis or pallor)
    - technical difficulties in monitoring ECG or systolic blood pressure
    - sustained ventricular tachycardia
- **risks**
  - death, myocardial infarction, arrhythmia, hemodynamic instability, and orthopedic injury (<1-5/10,000 supervised tests)

## NUCLEAR CARDIOLOGY

- **description**
  - myocardial perfusion imaging (MPI) with ECG-gated single photon emission computed tomography (SPECT), using radiolabelled tracer
  - evaluates myocardial viability, detects ischemia, and assesses perfusion and LV function simultaneously
  - predicts the likelihood of further cardiac event rates independent of the patient's history, examination, resting ECG, and stress ECG
  - often denoted as MIBI scan with reference to radiolabelled tracer (sestamibi)
  - stress with either treadmill or IV vasodilator stress (dipyridamole, adenosine, regadenoson)
  - images of the heart obtained during stress and at rest 3-4 h later
  - tracers
    - Thallium-201 ($^{201}$Tl, a $K^+$ analogue)
    - Technetium-99 ($^{99}$Tc)-labeled tracer (sestamibi/Cardiolite® or hexamibi/Myoview®)
- **indications**
  - to diagnose CAD in possible ACS patients with non-diagnostic ECG and negative serum biomarker
  - exercise MPI
    - when ECG cannot be interpreted appropriately due to LBBB or abnormal baseline ECG
    - intermediate pre-test probability with normal/equivocal exercise ECG
    - in patients with previous imaging whose symptoms have changed
    - to diagnose ischemia
  - dipyridamole/adenosine MPI
    - exercise testing is always preferred
    - pharmacological stress imaging test for patients who cannot exercise or do not want to hold cardiac meds (BB/CCBs)
    - same indication as exercise MPI
- **contraindications**
  - contraindications to exercise testing
  - vasodilators (i.e. adenosine, regadenoson, and dipyridamole) are contraindicated in patients with hypotension, sick sinus syndrome, high-degree AV block (in the absence of backup pacemaker capability), and reactive airways disease
  - pregnancy
- **risks**
  - radiation exposure

## STRESS ECHOCARDIOGRAPHY

- see *Echocardiography*, C12



**Most Commonly Used Treadmill Stress Test Protocols**

- The Bruce Protocol: 7 stage test with each stage lasting 3 min. With each successive stage, the treadmill increases in both speed (2.7 km/h to 9.6 km/h) and grade (10% with a 2% increase per stage up to 22%)
- The Modified Bruce, Modified Naughton Protocol: for older individuals or those with limited exercise capacity



**Important Contraindications to Exercise Testing**

- Acute MI, aortic dissection, pericarditis, myocarditis, PE
- Severe AS, arterial HTN
- Inability to exercise adequately



**Important Prognostic Factor**

Duke Treadmill Score (DTS)
Weighted Index Score

- Treadmill exercise time using standard Bruce protocol
- Maximum net ST segment deviation (depression or elevation)
- Exercise-induced angina provides diagnostic and prognostic information (such as 1 yr mortality)

DTS = exercise time – (5 x MaxST) – (4 x angina index)
Angina index: 0 (no angina), 1 (angina but not exercise-limiting), 2 (exercise-limiting angina)
DTS ≥5: 0.25% 1 yr mortality
DTS 4 to -10: 1.25% 1 yr mortality
DTS ≤ -11: 5.25% 1 yr mortality
*Ann Intern Med* 1987;106:793-800



Patients with normal imaging (nuclear perfusion or stress echo) studies at peak stress have a <1%/yr incidence of death or nonfatal MI and are thus often spared further invasive evaluation

# Cardiac Catheterization and Angiography

## Right Heart Catheterization (Swan-Ganz Catheter)

- **description**
  - also known as pulmonary artery catheterization
  - obtain direct measurements of central venous, right-sided intracardiac, pulmonary artery, and pulmonary artery occlusion pressures
  - can estimate cardiac output, systemic and pulmonary vascular resistance as well as mixed venous oxyhemoglobin saturation, oxygen delivery, and oxygen uptake
  - right atrial, right ventricular, and pulmonary artery pressures are recorded
  - can also be used to measure the Cardiac Index (CI), a measure of cardiac function
    - CI = CO/body surface area
    - 2.6-4.2 L/min/$m^2$ is considered normal while <1.8 L/min/$m^2$ usually means cardiogenic shock
  - pulmonary capillary wedge pressure (PCWP)
    - obtained by advancing the catheter to wedge in the distal pulmonary artery
    - records pressure measured from the pulmonary venous system
    - in the absence of pulmonary venous disease reflects left atrial pressure
- **indications**
  - unexplained or unknown volume status in shock
  - severe cardiogenic shock (e.g. acute valvular disease, suspected pericardial tamponade)
  - suspected or known pulmonary artery hypertension
  - severe underlying cardiopulmonary disease (e.g. congenital heart disease, left-to-right shunt, severe valvular disease, pulmonary hypertension) and undergoing corrective or other surgery
- **contraindications**
  - infection at the insertion site
  - presence of a right ventricular assist device
  - insertion during cardiopulmonary bypass
- **risks**
  - complications for diagnostic catheterization <1%
  - inadequate diagnostic procedures occur in <1% of cases
  - complications of insertion: atrial and/or ventricular arrhythmias (~3% of patients)
  - catheter misplacement or knotting (uncommon)
  - perforation of a cardiac chamber and rupture of a cardiac valve or the pulmonary artery (rare)
  - complications of catheterization: pulmonary artery rupture, pulmonary infarction, thromboembolic events, infection, and data misinterpretation
  - within 24 h of catheterization: death, MI, or stroke (0.2% to 0.3% of patients)

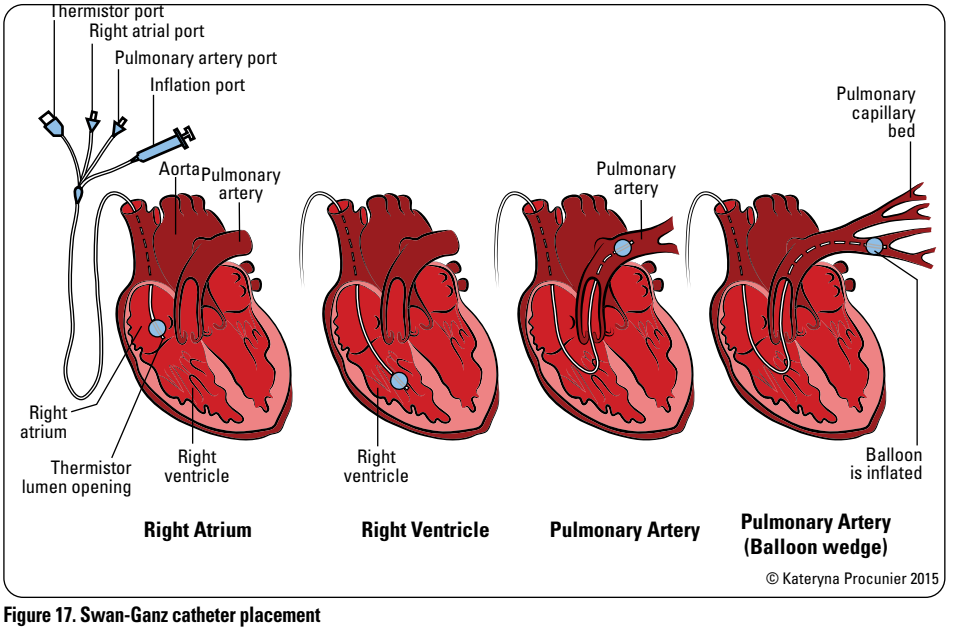



**Figure 17. Swan-Ganz catheter placement**

### Left Heart Catheterization

- **description**
  - accomplished by introducing a catheter into the brachial or femoral artery and advancing it through the aorta, across the aortic valve, and into the left ventricle
  - evaluates mitral and aortic valvular defects and myocardial disease
  - systolic and end-diastolic pressure tracings recorded
  - LV size, wall motion and ejection fraction can be assessed by injecting contrast into the LV (left ventriculography) via femoral/radial artery catheterization
  - cardiac output (measured by the Fick oxygen method or the indicator dilution method)
- **indications**
  - identification of the extent and severity of CAD and evaluation of left ventricular function
  - assessment of the severity of valvular or myocardial disorders (e.g. aortic stenosis or insufficiency, mitral stenosis or insufficiency, and various cardiomyopathies) to determine the need for surgical correction
  - collection of data to confirm and complement noninvasive studies
  - investigating CAD in patients with confusing clinical features or chest pain of uncertain origin
- **contraindications**
  - severe uncontrolled hypertension
  - ventricular arrhythmias
  - acute stroke
  - severe anemia
  - active gastrointestinal bleeding
  - allergy to radiographic contrast
  - acute renal failure
  - uncompensated congestive failure (patient cannot lie flat)
  - unexplained febrile illness or untreated active infection
  - electrolyte abnormalities (e.g. hyperkalemia)
  - severe coagulopathy
- **risks**
  - major complications for diagnostic catheterization (death, MI, stroke) <3 in 1000
  - minor complications e.g. vascular assess issue, kidney dysfunction <1 in 100
  - inadequate diagnostic procedures occur in <1% of cases

| Chambers | Pressure (systolic; mmHg) |
|---|---|
| Right atrium/central venous | 1-8 |
| Right ventricle | 1-8 (15-30) |
| Pulmonary artery | 4-12 (15-30) |
| Left atrium/ pulmonary capillary wedge | 4-12 |
| Left ventricle end diastolic | 4-12 |

## Coronary Angiography

- **description**
  - radiographic visualization of the coronary vessels after injection of radiopaque contrast media
  - coronary vasculature accessed via the coronary ostia
- **indications**
  - to define the coronary anatomy and the degree of luminal obstruction of the coronary arteries
  - to determine the presence and extent of obstructive CAD
  - to assess the feasibility and appropriateness of various forms of therapy, such as revascularization by percutaneous or surgical interventions
  - can be used when the diagnosis of CAD is uncertain and cannot be excluded by noninvasive techniques
- **contraindications**
  - severe renal failure due to contrast agent toxicity (must check patient's renal status due to contrast agent toxicity)
- **risks**
  - major complications for diagnostic catheterization (death, MI, stroke) <3 in 1000
  - minor complications e.g. vascular assess issue, kidney damage <1/100

**ACC/AHA 2011 Recommended Indications for Coronary Angiography**

- Disabling (CCS classes III and IV) chronic stable angina despite medical therapy
- High-risk criteria on clinical assessment or non-invasive testing
- Serious ventricular arrhythmia or CHF
- Uncertain diagnosis or prognosis after non-invasive testing
- Inability to undergo non-invasive testing

**Coronary Angiography**
Gold standard for localizing and quantifying CAD

Hemodynamically significant stenosis is defined as 70% or more narrowing of the luminal diameter

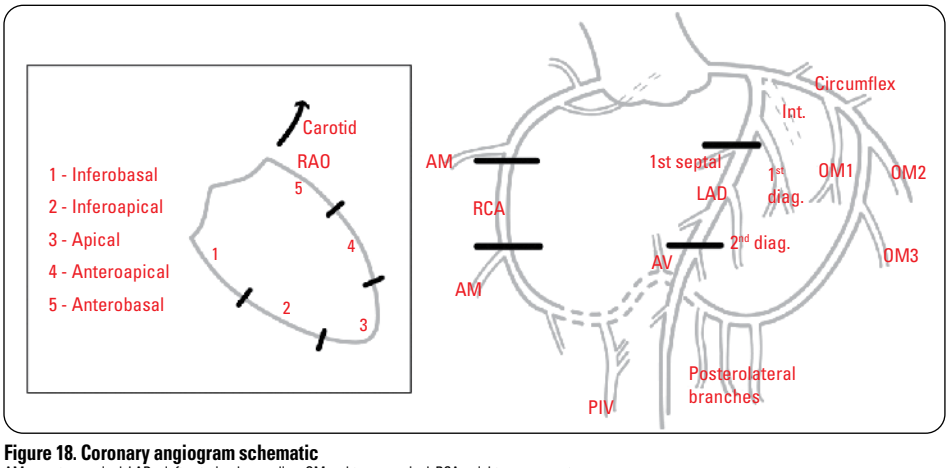



**Figure 18. Coronary angiogram schematic**
AM = acute marginal; LAD = left anterior descending; OM = obtuse marginal; RCA = right coronary artery

### Diagnostic Catheterization

- provocative pharmacological agents can be used to unmask pathology
  - fluid loading may unmask latent pericardial constriction
  - afterload reduction or inotropic stimulation may be used to increase the outflow tract gradient in HCM
  - coronary vasoreactive agents (e.g. methylergonovine, acetylcholine)
  - a variety of pulmonary vasoreactive agents in primary pulmonary HTN (e.g. oxygen, calcium channel blockers, adenosine, nitric oxide, prostacyclin)

## Contrast-Enhanced CT Coronary Angiography

- **description**: fast ECG-synchronized multi-slice CT image acquisition in the heart to enable non-invasive imaging of the coronary arterial tree
- **indications**: often used to assess coronary artery and previous graft stenosis/viability that could not be seen during coronary angiography
- sensitivity = 85%, specificity = 90% for the diagnosis of obstructive coronary disease with >50% stenosis
- **contraindications**: allergy to contrast dye; severe renal dysfunction
- **risks**: radiation exposure

## Magnetic Resonance Imaging

- **description**
  - offers high spatial resolution, eliminates the need for iodinated contrast, and does not involve exposure to ionizing radiation
- **indications**
  - valuable in assessment of congenital cardiac anomalies, abnormalities of the aorta, assessment of viable myocardium, and assessment of cardiomyopathies
- **contraindications**
  - metallic foreign bodies/implants, kidney dysfunction due to gadolinium contrast medium
- **risks**
  - hazards posed by certain metallic devices inside patients

# CARDIAC DISEASE

# Arrhythmias

## Mechanisms of Arrhythmias

### Alterations in Impulse Formation

**A. Normal Automaticity**

- impulses from the SA node, caused by spontaneous depolarization, result in the basic cardiac pacemaker function. "Downstream" cells in the AV node and Purkinje fibres also depolarize spontaneously, but at a slower rate; they serve as the "backup" pacemaking cells if the upstream rate is slower than the more distal spontaneous rate.
- normal automaticity is influenced by:
  - neurohormonal tone (sympathetic tone increases and parasympathetic tone decreases spontaneous firing rate and thus heart rate)
  - myocardial ischemia/infarction or other cardiac pathology (e.g. heart failure) may alter heart rate via these mechanisms
  - abnormal metabolic conditions (e.g. hypoxia, acidosis, hypothermia)
  - electrolyte abnormalities, especially hyperkalemia which slows heart rate
  - drugs (e.g. digitalis, beta blockers, calcium channel blockers)

**B. Abnormal Automaticity due to Triggered Activity (due to Afterdepolarizations)**

**1. Early Afterdepolarizations**

- during the terminal plateau or repolarization phases of action potential
- consequence of the membrane potential transiently becoming more positive during repolarization (depolarization interrupting repolarization)
  - these are called EADs and DADs (early and delayed afterdepolarization, respectively)
- may result in self-maintaining oscillations of depolarization, giving rise to action potentials thereby generating a tachyarrhythmia (e.g. new baseline voltage is greater than threshold, which automatically triggers a new action potential after the refractory period ends)
- EADs are the basis for the arrhythmias associated with QT prolongation, either congenital or acquired; termed "Torsades de Pointes"



**Sinus Arrhythmia (SA)**

- Normal P waves, with variation of the P-P interval by >120 msec due to varying rate of SA node depolarization

**Respiratory SA**

- Seen more often in young adults (<30 yr old)
- Normal, physiologic results from changes in autonomic tone during respiratory cycle
- Rate increases with inspiration, slows with expiration

**Non-Respiratory SA**

- Seen more often in the elderly
- Can occur in the normal heart; if marked may be due to sinus node dysfunction (e.g. in heart disease or after digitalis toxicity)
- Usually does not require treatment

**2. Delayed Afterdepolarizations**
- occur after the action potential has fully repolarized, but before the next usual action potential
- commonly occurs in situations of high intracellular calcium (e.g. digitalis intoxication, ischemia) or during enhanced catecholamine stimulation (e.g. "twitchy" pacemaker cells)

## Alterations in Impulse Conduction

**A. Re-Entry Circuits**
- the presence of self-sustaining re-entry circuit causes rapid repeated depolarizations in a region of myocardium (see Figure 26, C20, for an example in the context of AV nodal re-entrant tachycardia)
- the conditions necessary for reentry include block of an impulse into a region of the heart that is refractory (non-excitable tissue or because of local functional block, where the impulse encounters tissue still in its refractory period), followed by "reentry" of the impulse around a region of block to the site of origin, forming a complete reentry circuit
  - e.g. myocardium that is infarcted/ischemic will consist of non-excitable and partially excitable zones which will promote the formation of re-entry circuits

**B. Conduction Block**
- ischemia, fibrosis, trauma, and drugs can cause transient or permanent, unidirectional or bidirectional block
- most common cause of block is due to refractory myocardium (cardiomyocytes are in refractory period or zone of myocardium unexcitable due to fibrosis)
- cells in the conduction system distal to the block can assume pacemaking control if the block occurs along the specialized conduction system
- conduction block can lead to bradycardia

**C. Bypass Tracts**
- normally, the only electrical connection between atria (A) and ventricles (V) is the AV node and penetrating Bundle of His
- an accessory bypass tract is a direct connection between atrium and ventricle, histologically similar to atrial tissue, through the valve ring which is impervious to electrical impulses
  - see *Pre-Excitation Syndromes*, C21

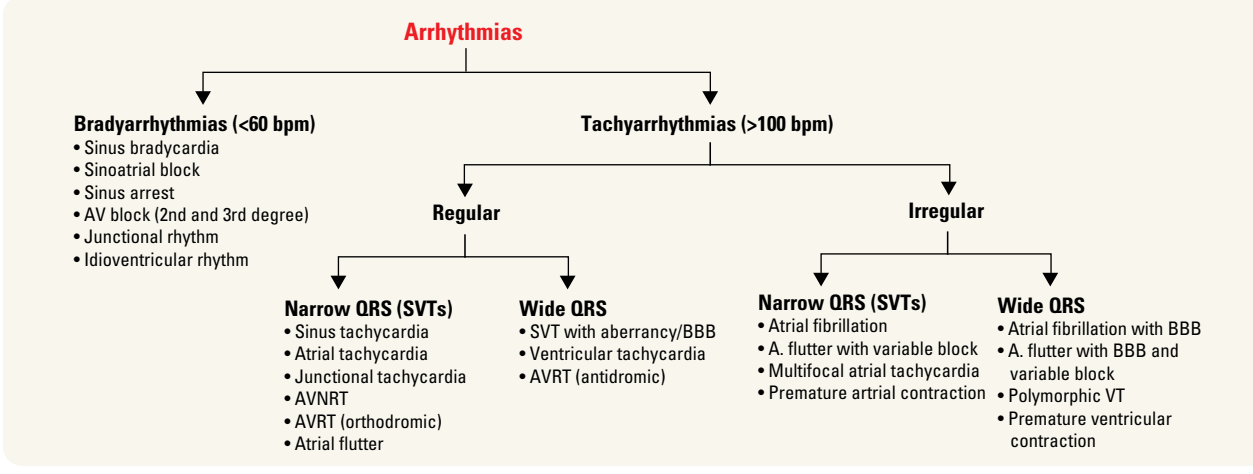



**Figure 19. Clinical approach to arrhythmias**

# Bradyarrhythmias

## 1. SA NODAL DYSFUNCTION

### A. Sinus Bradycardia

P axis normal (P waves positive in I and aVF)
Rate <60 bpm; marked sinus bradycardia (<50 bpm)
May be seen in normal adults, particularly athletes, and in elderly individuals
Increased vagal tone or vagal stimulation; drugs (e.g. β-blockers, calcium channel blockers); ischemia/infarction

Atropine; pacing for sick sinus syndrome

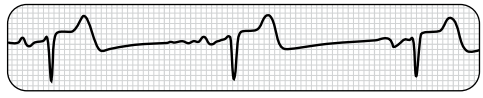


**Figure 20. Sinus bradycardia**

## 2. AV CONDUCTION BLOCKS

### A. First Degree AV Block

Prolonged PR interval (>220 msec)
Frequently found among otherwise healthy adults

No treatment required

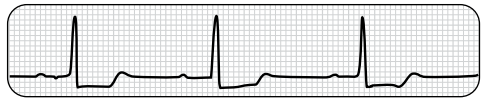


**Figure 21. First degree AV block**

### B. Second Degree AV Block: Type I (Mobitz I)

A gradual prolongation of the PR interval precedes the failure of conduction of a P wave (Wenckebach phenomenon)
AV block is usually in AV node (proximal) triggers (usually reversible): increased vagal tone (e.g. following surgery), RCA-mediated ischemia

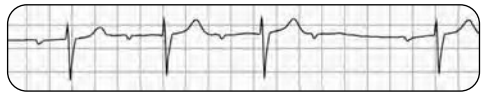


**Figure 22. Second degree AV block with Wenckebach phenomenon (Mobitz I) (4:3 conduction) (lead V1)**

### B. Second Degree AV Block: Type II (Mobitz II)

The PR interval is constant; there is an abrupt failure of conduction of a P wave
Often associated with distal conduction system disease (bundle branch block)
AV block is usually distal to the AV node (i.e. bundle of His); increased risk of high grade or 3rd degree AV block

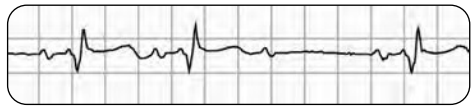


**Figure 23. Second degree AV block (Mobitz II) (3:2 conduction) (lead V1)**

### B. Third Degree AV Block

Complete failure of conduction of the supraventricular impulses to the ventricles; ventricular depolarization initiated by an escape pacemaker distal to the block
Wide or narrow QRS, P-P and R-R intervals are constant, variable PR intervals; no relationship between P waves and QRS complexes (P waves "marching through")

Management (see *Electrical Pacing*, C24)



**Figure 24. Third degree AV block (complete heart block) (lead II)**

# Supraventricular Tachyarrhythmias

## Presentation for SVT (and Pre-Excitation Syndromes)

- presentation can include: palpitations, dizziness, dyspnea, chest discomfort, presyncope/syncope
- may precipitate CHF, hypotension, or ischemia in patients with underlying cardiovascular disease
- untreated tachycardias of long duration (days) can cause tachycardia induced cardiomyopathy (rare, potentially reversible with treatment of SVTs)
- arrhythmias involving the AV node (AVNRT and AVRT) may terminate spontaneously, after vagal stimulation, or adenosine treatment

## Supraventricular Tachyarrhythmias

- tachyarrhythmias that originate in the atria or AV junction
- this term is used when a more specific diagnosis of mechanism and site of origin cannot be made
- characterized by narrow QRS unless there is pre-existing bundle branch block or aberrant ventricular conduction (abnormal conduction due to a change in cycle length)

## 1. Sinus Tachycardia

- sinus rhythm with rate >100 bpm
- occurs in normal subjects with increased sympathetic tone (e.g. exercise, anxiety, pain, pregnancy), alcohol use, caffeinated beverages, drugs (e.g. β-adrenergic agonists, anticholinergic drugs)
- systemic etiology: fever, hypotension, hypovolemia, anemia, thyrotoxicosis, CHF, MI, shock, pulmonary embolism
- treatment: treat underlying disease; consider β-blocker if symptomatic, calcium channel blocker if β-blockers contraindicated; ivabradine may be considered as an alternative agent for inappropriate sinus tachycardia

## 2. Premature Beats
- premature atrial contraction
  - ectopic supraventricular beat originating in the atria
  - P wave morphology of the PAC usually differs from that of a normal sinus beat
- junctional premature beat
  - ectopic supraventricular beat that originates in the vicinity of the AV node
  - P wave is usually not seen or an inverted P wave is seen and may be before or closely follow the QRS complex (referred to as a retrograde, or "traveling backward" P wave)
- treatment usually not required

## 3. Atrial Flutter
- rapid, regular atrial depolarization from a macro re-entry circuit within the atrium (most commonly right atrium)
- atrial rate 250-350 bpm, usually 300 bpm
- AV block usually occurs; it may be fixed (e.g. 2:1, 3:1, 4:1, etc.) or variable
- etiology: hypertension, cardiomyopathy , in association with atrial fibrillation; less often, CAD, thyrotoxicosis, mitral valve disease, cardiac surgery, COPD, PE, pericarditis
- ECG: sawtooth flutter waves (most common type of flutter, called "isthmus dependent, typical flutter) in inferior leads (II, III, aVF); narrow QRS (unless aberrancy); commonly seen as 2:1 block with HR of 150
- in atrial flutter with 2:1 block, carotid sinus massage (first check for bruits), Valsalva maneuver, or adenosine may decrease AV conduction and allow flutter waves to be more easily seen
- treatment of acute atrial flutter
  - if unstable (e.g. hypotension, CHF, angina): electrical cardioversion
  - if stable:
    1. rate control: β-blocker, diltiazem, verapamil, or digoxin
    2. chemical cardioversion: sotalol, amiodarone, type I antiarrhythmics, or electrical cardioversion
  - anticoagulation guidelines same as for patients with AFib
- treatment of long-term AFib includes antiarrhythmics and radiofrequency (RF) ablation (success rate dependent on site of origin of atrial flutter)

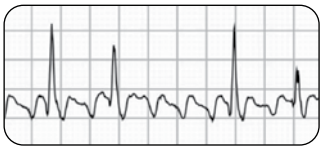


**Figure 25. Atrial flutter with variable block**

## 4. Multifocal Atrial Tachycardia (MAT)
- irregular rhythm caused by presence of 3 or more atrial foci (may mimic AFib)
- atrial rate 100-200 bpm
  - 3 or more distinct P wave morphologies and PR intervals vary, some P waves may not be conducted
- occurs more commonly in patients with COPD and hypoxemia; less commonly in patients with hypokalemia, hypomagnesemia, sepsis, theophylline, or digitalis toxicity
- treatment: treat the underlying cause; calcium channel blockers may be used (e.g. diltiazem, verapamil), β-blockers may be contraindicated because of severe pulmonary disease
- no role for electrical cardioversion, antiarrhythmics, or ablation

## 5. Atrial Fibrillation
- see *CCS Atrial Fibrillation Guidelines 2016* for details (free mobile app – iCCS available on iOS and Android)
- most commonly sustained arrhythmia
- incidence increases with age (10% of population >80 yr)
- symptoms: palpitations, fatigue, dyspnea, syncope, may precipitate or worsen heart failure
- **classification**
  - lone: generally occurs in persons <65 yr and in whom no clinical or echocardiographic causes are found
  - nonvalvular: not caused by valvular disease, prosthetic heart valves, or valve repair
  - paroxysmal: episodes that terminate spontaneously
  - persistent: AFib sustained for more than 7 d or AFib that terminates only with cardioversion
  - permanent/chronic: continuous AFib that is unresponsive to cardioversion or in which clinical judgement has led to a decision not to pursue cardioversion
  - recurrent: two or more episodes of AFib
  - secondary: caused by a separate underlying condition or event (e.g. MI, cardiac surgery, pulmonary disease, hyperthyroidism)
  - may be associated with thromboembolic events (stroke risk can be assessed by CHADS2 score in nonvalvular AFib; CHADS2-VASc if the former gives a score of 0 or 1)
- **initiation**
  - single circuit re-entry and/or ectopic foci, mostly arising from the pulmonary veins, act as aberrant generators producing atrial tachycardia (350-600 bpm), which leads to multiple re-entry circuity (microreentry)
  - impulses conduct irregularly across the atrial myocardium to give rise to fibrillation
  - in most cases, ectopic foci have also been mapped to the pulmonary vein ostia and can be ablated
- **maintenance**
  - the tachycardia causes atrial structural and electrophysiological remodelling changes that further promote AFib; the longer the patient is in AFib the more difficult it is to convert back to sinus rhythm
- **consequences**
  - the AV node irregularly filters incoming atrial impulses producing an irregular ventricular response usually <200 bpm, and the tachycardia leads to suboptimal cardiac output
  - fibrillatory conduction of the atria promotes blood stasis increasing the risk of thrombus formation
    - AFib is an important risk factor for stroke

**Atrial Fibrillation – AFFIRM Trial**
NEJM 2002;347:1825-1833
**Study:** Randomized, multicentre trial with mean follow-up of 3.5 yr.
**Population:** 4060 patients (mean age 70 yr, 61% male, 89% white) with AF and a high risk of stroke or death.
**Intervention:** Rate control (β-blockers, calcium channel blockers, or digoxin alone or in combination) vs. rhythm control (antiarrhythmic drug chosen by the treating physician).
**Primary Outcome:** All cause mortality.
**Results:** There was no difference in mortality or disabling stroke, anoxic encephalopathy, major bleeding, and cardiac arrest between the two groups. There were more incidents of hospitalizations (80.1% vs. 73%, p<0.001) and adverse events (Torsades de Pointes (12 vs. 2, p=0.007), pulseless or bradycardic arrest (9 vs. 1, p=0.01), pulmonary event (108 vs. 24, p<0.001), gastrointestinal event (127 vs. 35, p<0.001), prolonged QT interval (31 vs. 4, p≤0.001), bradycardia (105 vs. 64, p=0.001) in the rhythm-control group.
**Conclusion:** Rate-control was as effective as rhythm-control in AF and was better tolerated. There were more hospitalization incidents in the rhythm-control group.

**Table 5. CHADS2 Risk Prediction for Non-Valvular AFib**

| Risk Factor | Points | CHADS2 Score | Stroke Risk (%/Yr) |
|---|---|---|---|
| **Congestive Heart Failure** | 1 | 0 | 1.9 (low) |
| **Hypertension** | 1 | 1 | 2.8 (low-mod) |
| **Age >75** | 1 | 2-3 | 4.0-5.9 (mod) |
| **Diabetes** | 1 | 4-6 | 8.5-18.2 (high) |
| **Stroke/TIA (prior)** | 2 | | |

JAMA 2001;285:2864-70 and Can J Cardiol 2014 Oct;30(10):1114-30.

- **ECG findings**
  - no organized P waves due to rapid atrial activity (350-600 bpm) causing a chaotic fibrillatory baseline
  - irregularly irregular ventricular response (typically 100-180 bpm), narrow QRS (unless aberrancy or previous BBB)
  - wide QRS complexes due to aberrancy may occur following a long-short cycle sequence ("Ashman phenomenon")
  - loss of atrial contraction, thus no "a" wave seen in JVP, no S4 on auscultation

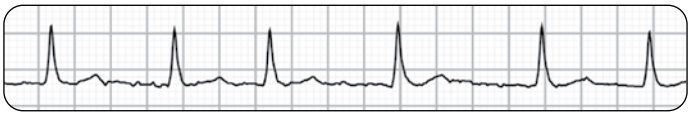


**Figure 26. Atrial fibrillation (lead II)**

- management (adapted from CCS Atrial Fibrillation Guidelines 2016 & 2018)
  - primary goal is symptom control
  - **major objectives (RACE)**: all patients with AFib (paroxysmal, persistent, or permanent), should be stratified using a predictive index for stroke risk and for the risk of bleeding, and most patients should receive either an oral anticoagulant or ASA
    1. **R**ate control: β-blockers, diltiazem, verapamil (in patients with heart failure: digoxin, amiodarone)
       - digoxin can be considered as a therapeutic option to achieve rate control in patients whose response to β-blockers and/or calcium channel blockers is inadequate, contraindicated or not tolerated
    2. **A**nticoagulation: use either warfarin or novel oral anticoagulant (NOACs) e.g. apixaban, dabigatran, rivaroxaban, edoxaban to prevent thromboembolism
       - for patients with non-valvular AF (NVAF): oral anticoagulant (OAC) is recommended for most patients aged >65 yr or $CHADS_2$ ≥1
         - ASA 81 mg is recommended only for patients with none of the risk outlined in the CCS algorithm (age <65 and no $CHADS_2$ risk factors) who also have arterial disease (coronary, aortic, or peripheral)
         - novel oral anticoagulant (NOAC) is to be used in preference to warfarin
    3. **C**ardioversion (electrical)
       - if AFib <48 h, can usually cardiovert without anticoagulation
       - if AFib >48 h, anticoagulate for 3 wk prior and 4 wk after cardioversion due to risk of unstable intra-atrial thrombus
       - if patient unstable (hypotensive, active angina due to tachycardia, uncontrolled heart failure) should cardiovert immediately
    4. **E**tiology
       - HTN, obesity, sleep apnea, CAD, valvular disease, pericarditis, cardiomyopathy, myocarditis, ASD, post-operative, PE, COPD, thyrotoxicosis, sick sinus syndrome, alcohol ("holiday heart")
       - may present in young patients without demonstrable disease ("lone AFib") and in the elderly without underlying heart disease
  - studies of patients with AFib suggest that there is no difference in long-term survival when treating patients with a rhythm-control versus rate-control strategy
  - many patients with a significant underlying structural heart lesion (e.g. valve disease, cardiomyopathy) will not tolerate AFib well (since may be dependent on atrial kick) and these patients should be cardioverted (chemical or electrical) as soon as possible
  - **newly discovered AFib**
    - anticoagulants may be beneficial if high risk for stroke
    - if the episode is self-limited and not associated with severe symptoms, no need for antiarrhythmic drugs
    - if AFib persists, 2 options:
      1. rate control and anticoagulation (as indicated above)
      2. cardioversion (as indicated above)
    - recurrent or permanent AFib
    - if episodes are brief or minimally symptomatic, antiarrhythmic drugs may be avoided; rate control and anticoagulation are appropriate
    - patients who have undergone at least one attempt to restore sinus rhythm may remain in AFib after recurrence; permanent AFib may be accepted (with rate control and antithrombotics as indicated by $CHADS_2$ score) in certain clinical situations
    - if symptoms are bothersome or episodes are prolonged, antiarrhythmic drugs should be used
      - no or minimal heart disease: flecainide, propafenone once proven to have no underlying CAD (may consider exercise stress testing)

**Lenient versus Strict Rate Control in Patients with Atrial Fibrillation**
NEJM 362:1363-1373
**Study:** Randomized, multi-centre Netherlands prospective study, follow-up for at least 2 yr
**Population:** 614 patients with permanent atrial fibrillation.
**Intervention:** Lenient control (resting HR <110 bpm) or strict control (resting HR <80 bpm)
**Primary Outcomes:** Death from cardiovascular causes, hospitalization for heart failure, and stroke, systemic embolism, bleeding, and life-threatening arrhythmic events.
**Results:** Goal of the study was to establish whether lenient control was equivalent to strict control for prevention of primary outcomes. Resulting hazard ratios were not significantly different between the treatment groups (P = 0.001). Frequencies of hospitalization and adverse effects were also similar. More patients were able to maintain lenient targets (97.7%) compared to strict targets (67%).
**Conclusion:** Lenient control was equivalent to strict control for prevention of primary outcomes in patients with atrial fibrillation. Furthermore, lenient control was more easily achieved.

- LV dysfunction: amiodarone
- CAD: β-blockers, amiodarone
- if antiarrhythmic drugs fail or are not tolerated, can consider RF ablation for rhythm/symptom control

### 6. AV NODAL RE-ENTRANT TACHYCARDIA (AVNRT)

- re-entrant circuit using dual pathways (fast conducting β-fibres and slow conducting α-fibres) within or near the AV node; often found in the absence of structural heart disease
  - cause is commonly idiopathic, although familial AVNRT has been reported
- sudden onset and offset, patients often describe "neck pounding" and "shirt flapping"
- fast regular rhythm: rate 150-250 bpm
- usually initiated by a supraventricular or ventricular premature beat
- AVNRT accounts for 60-70% of all paroxysmal SVTs
- retrograde P waves may be seen but are usually lost in the QRS complex
- treatment
  - acute: Valsalva maneuver or carotid sinus pressure technique, adenosine is first choice if unresponsive to vagal maneuvers; if no response, try metoprolol, digoxin, diltiazem, electrical cardioversion if patient hemodynamically unstable (hypotension, angina, or CHF)
  - long-term: 1st line – radiofrequency ablation (>98% cure rate and << 1% complication rate), β-blocker, diltiazem, digoxin; 2nd line – flecainide, propafenone

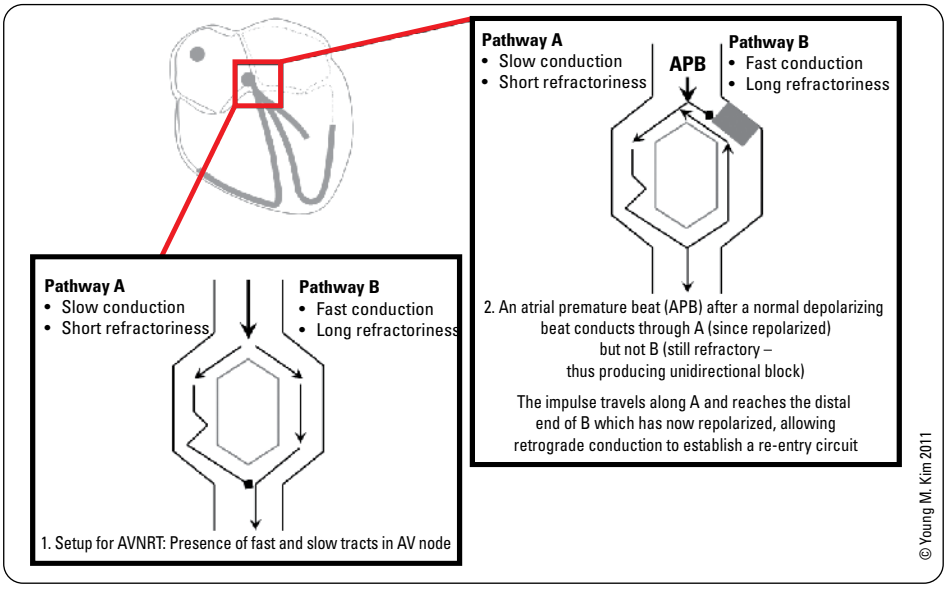



**Figure 28. Mechanism for AVNRT**

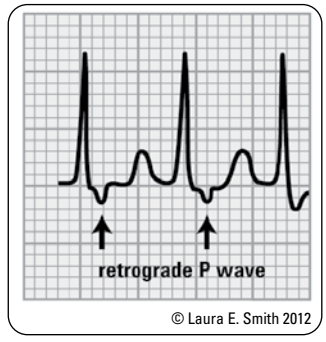



**Figure 27. AVNRT**

N.B. Refer to ECG Made Simple for further discussion and an animation of the mechanism (www.ecgmadesimple.com)

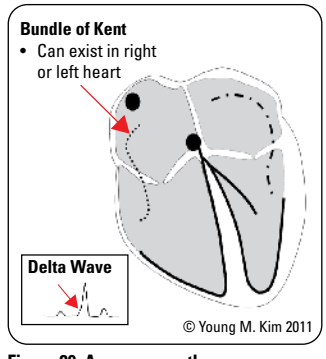



**Figure 29. Accessory pathway conduction in WPW.** Early ventricular activation leads to the appearance of a delta wave (slurred upstroke of the QRS) on the ECG before usual conduction across the AV node

## Pre-Excitation Syndromes

- refers to a subset of SVTs mediated by an accessory pathway which can lead to ventricular pre-excitation

### Wolff-Parkinson-White Syndrome (WPW)

- congenital defect present in 1.5-2/1000 of the general population
- an accessory conduction tract (Bundle of Kent; can be in right or left atrium) abnormally allows early electrical activation of part of one ventricle
- impulses travel at a greater conduction velocity across the Bundle of Kent thereby effectively 'bypassing' AV node
- since the ventricles are activated earlier, the ECG shows early ventricular depolarization in the form of initial slurring of the QRS complex – the so-called "delta wave"
- atrial impulses that conduct to the ventricles through both the Bundle of Kent and the normal AV node/His-Purkinje system generate a broad "fusion complex"
- ECG features of WPW
  - PR interval <120 msec
  - delta wave: slurred upstroke of the QRS (the leads with the delta wave vary with site of bypass)
  - widening of the QRS complex due to premature activation
  - secondary ST segment and T wave changes
  - tachyarrhythmias may occur – most often AVRT and AFib

### AFib in WPW Patients

- AFib is the index arrhythmia in up to 20% of patients with WPW syndrome
  - usually intermittent rather than persistent or permanent
- rapid atrial depolarizations in AFib are conducted through the bypass tract which is not able to filter impulses like the AV node can and thus the ventricular rate becomes extremely rapid (>200 bpm) and the QRS complex widens

- treatment: electrical cardioversion, IV procainamide, or IV amiodarone
  - do not use drugs that slow AV node conduction (digoxin, β-blockers) as this may cause preferential conduction through the bypass tract and precipitate VF
  - long-term: ablation of bypass tract if possible

### AV Re-Entrant Tachycardia

- re-entrant loop via accessory pathway and normal conduction system
- initiated by a premature atrial or ventricular complex
- **orthodromic AVRT**: stimulus from a premature complex travels up the bypass tract (V to A) and down the AV node (A to V) with narrow QRS complex (no delta wave because stimulus travels through normal conduction system)
- comprises 95% of the reentrant tachycardias associated with WPW syndrome
- **antidromic AVRT**: more rarely the stimulus goes up the AV node (V to A) and down the bypass tract (A to V); wide and abnormal QRS as ventricular activation is only via the bypass tract
- **treatment**
  - acute: similar to AVNRT except avoid long-acting AV nodal blockers (e.g. digoxin and verapamil)
  - long-term: for recurrent arrhythmias ablation of the bypass tract is recommended
  - drugs such as flecainide and procainamide can be used

## Ventricular Tachyarrhythmias

### Premature Ventricular Contraction (PVC) or Ventricular Premature Beat (VPB)

- QRS width >120 msec, no preceding P wave, bizarre QRS morphology
- origin: LBBB morphology of VT = RV origin; RBBB morphology of VT = LV origin
- PVCs may be benign but are usually significant in the following situations:
  - consecutive (≥3 = VT) or multiform (varied origin)
  - PVC falling on the T wave of the previous beat ("R on T phenomenon"): may precipitate ventricular tachycardia or VF
- risk of sustained arrhythmia depends on the clinical situation (i.e. MI, HF), not the PVCs themselves

### Accelerated Idioventricular Rhythm

- ectopic ventricular rhythm with rate 50-100 bpm
- more frequently occurs in the presence of sinus bradycardia and is easily overdriven by a faster supraventricular rhythm
- frequently occurs in patients with acute MI or other types of heart disease (i.e. cardiomyopathy, hypertensive, valvular) but it does not affect prognosis and does not usually require treatment

### Ventricular Tachycardia (VT)

- 3 or more consecutive ectopic ventricular complexes
  - rate >100 bpm (usually 140-200)
  - ventricular flutter: if rate >200 bpm and complexes resemble a sinusoidal pattern
  - "sustained VT" if it lasts longer than 30s
  - ECG characteristics: wide regular QRS tachycardia (QRS usually >140 msec)
  - AV dissociation; bizarre QRS pattern
  - also favour Dx of VT: left axis or right axis deviation, nonspecific intraventricular block pattern, monophasic or biphasic QRS in V1 with RBBB, QRS concordance in V1-V6
  - occasionally during VT supraventricular impulses may be conducted to the ventricles generating QRS complexes with normal or aberrant supraventricular morphology ("ventricular capture") or summation pattern ("fusion complexes")
  - by themselves, nonsustained VT not dangerous but may indicate higher than usual risk of subsequent sustained VT, especially with structural heart disease
- **monomorphic VT**
  - identical complexes with uniform morphology
  - more common than polymorphic VT
  - typically result from intraventricular re-entry circuit, may be idiopathic without any structural heart disease
  - potential causes: chronic infarct related scarring, cardiomyopathies, myocarditis, arrhythmogenic right ventricular dysplasia, idiopathic, drugs (e.g. cocaine), electrolyte disturbances
- **polymorphic VT**
  - complexes with constantly changing morphology, amplitude, and polarity
  - more frequently associated with hemodynamic instability due to faster rates (typically 200-250 bpm) vs. monomorphic VT
  - potential causes: acute MI, severe or silent ischemia, and predisposing factors for QT prolongation, dilated cardiomyopathies
- **treatment**
  - sustained VT (>30 s) is an emergency requiring immediate treatment
  - hemodynamic compromise: electrical cardioversion
  - no hemodynamic compromise: electrical cardioversion, amiodarone, type Ia agents (procainamide, quinidine)

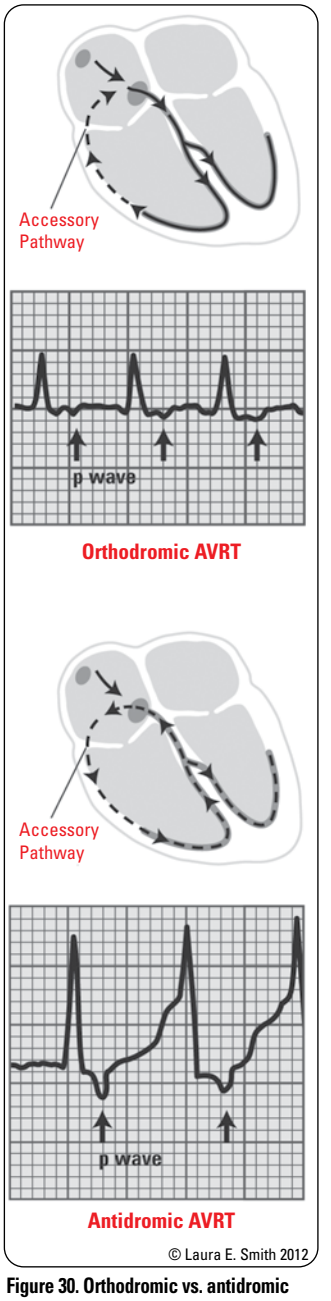



**Figure 30. Orthodromic vs. antidromic AVRT**

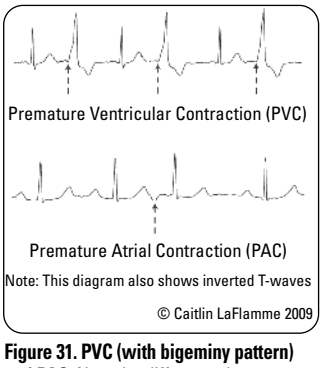



**Figure 31. PVC (with bigeminy pattern) and PAC.** Note the difference between the normal QRS/T wave and the PVC-generated QRS/T wave

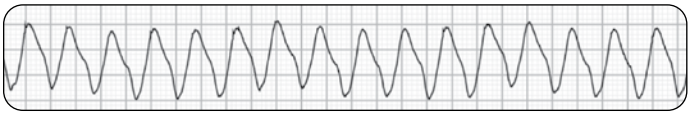


**Figure 32. Ventricular tachycardia (monomorphic)**

**Table 6. Wide Complex Tachycardia: Clues for Differentiating VT vs. SVT with Aberrancy***

| Clinical Clues | | ECG Clues | |
|---|---|---|---|
| Presenting symptoms | Not helpful | AV dissociation | VT |
| History of CAD and previous MI | VT | Capture or fusion beats | VT |
| Physical exam | | QRS width >140 msec | VT |
| Cannon "a" waves<br>Variable S1 | VT | Extreme axis deviation (left or right superior axis) | VT |
| Carotid sinus massage/ adenosine terminates arrhythmia | SVT** | Positive QRS concordance (R wave across chest leads) | VT |
| | | Negative QRS concordance (S wave across chest leads) | May suggest VT |
| | | Axis shift during arrhythmia | VT (polymorphic) |

***If patient >65 yr and previous MI or structural heart disease, then chance of VT >95%**
**May terminate VT in some patients with no structural heart disease

**Arrhythmias that May Present as a Wide QRS Tachycardia**
- VT
- SVT with aberrant conduction (rate related)
- SVT with preexisting BBB or nonspecific intraventricular conduction defect
- AV conduction through a bypass tract in WPW patients during an atrial tachyarrhythmia (e.g. atrial flutter, atrial tachycardia)
- Antidromic AVRT in WPW patients (see *Pre-Excitation Syndromes*, C21)

## Torsades de Pointes

- a variant of polymorphic VT that occurs in patients with baseline QT prolongation – "twisting of the points"
- looks like usual VT except that QRS complexes "rotate around the baseline" changing their axis and amplitude
- ventricular rate >100 bpm, usually 150-300 bpm
  - usual onset after a post PVC pause ("pause dependent" QT prolongation associated)
- **etiology**: predisposition in patients with prolonged QT intervals
  - congenital long QT syndromes
  - drugs: e.g. class IA (quinidine), class III (sotalol), phenothiazines (TCAs), erythromycin, quinolones, antihistamines
  - electrolyte disturbances: hypokalemia, hypomagnesemia
  - nutritional deficiencies causing above electrolyte abnormalities
- **treatment**: IV magnesium, temporary pacing, isoproterenol and correcting the underlying cause of prolonged QT, electrical cardioversion if hemodynamic compromise



**Figure 33. Torsades de pointes**

## Ventricular Fibrillation (VFib)

- chaotic ventricular arrhythmia, with very rapid irregular ventricular fibrillatory waves of varying morphology
- terminal event, unless advanced cardiac life-support (ACLS) procedures are promptly initiated to maintain ventilation and cardiac output, and electrical defibrillation is carried out
- most frequent cause of sudden death
- refer to ACLS algorithm for complete therapeutic guidelines

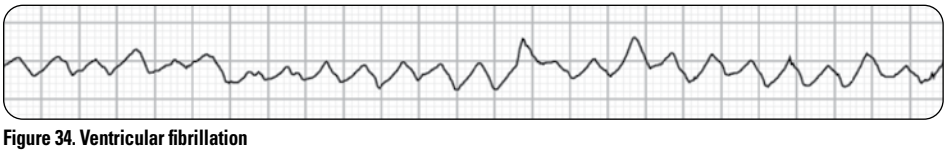


**Figure 34. Ventricular fibrillation**

# Sudden Cardiac Arrest

### Definition
- unanticipated, non-traumatic cardiac death in a stable patient which occurs within 1 h of symptom onset; VFib is most common cause

### Etiology
- primary cardiac pathology
  - ischemia/MI
  - cardiomyopathy with LV dysfunction
  - severe ventricular hypertrophy
  - HCM
  - AS
  - congenital heart disease e.g. arrhythmogenic right ventricular dysplasia
  - mutations in cardiac ion channels e.g. long QT syndrome, Brugada syndrome

### Management
- acute: resuscitate with prompt CPR and defibrillation
- investigate underlying cause (cardiac catheterization, electrophysiologic studies, echocardiography)
- treat underlying cause
- antiarrhythmic drug therapy: amiodarone, β-blockers
- implantable cardioverter defibrillator (ICD)
- refer to ACLS guidelines (see Anesthesia and Perioperative Medicine, A30)

**CCS Consensus Conference 2003: Assessment of the Cardiac Patient for Fitness to Drive and Fly – Executive Summary**
Can J Cardiol 2004;20:1313-1323
In both primary and secondary prevention ICD patients with private driving licenses, no restrictions to drive directly following implantation or an inappropriate shock are warranted. However, following an appropriate shock these patients are at an increased risk to cause harm to other road users and therefore should be restricted to drive for a period of 2 and 4 mo, respectively. In addition, all ICD patients with commercial driving licenses have a substantial elevated risk to cause harm to other road users during the complete follow-up after both implantation and shock and should therefore be restricted to drive permanently. (A complete set of easy to access CCS Drive and Fly guidelines is available in the iCCS App available for iOS and Android platforms)

# Electrophysiology Studies

- invasive test for the investigation and treatment of cardiac rhythm disorders using intracardiac catheters
- provide detailed analysis of the arrhythmia mechanism and precise site of origin when ECG data are nondiagnostic or unobtainable
- bradyarrhythmias: define the mechanisms of SA node dysfunction and localize site of AV conduction block
- tachyarrhythmias: map for possible ablation or to assess inducibility of VT

# Electrical Pacing

- the decision to implant a pacemaker usually is based on symptoms of a bradyarrhythmia or tachyarrhythmia in the setting of heart disease

### Pacemaker Indications
- SA node dysfunction (most common): symptomatic bradycardia ± hemodynamic instability
- common manifestations include: syncope, presyncope, or severe fatigue
- SA node dysfunction is commonly caused by: intrinsic disease within the SA node (e.g. idiopathic degeneration, fibrosis, ischemia, or surgical trauma), abnormalities in autonomic nervous system function, and drug effects
- AV nodal-infranodal block: Mobitz II, complete heart block

### Pacemaker Complications
- complications related to surgical implantation include venous access (pneumothorax, hemothorax, air embolism), pacemaker leads (perforation, malposition), pocket hematomas and infection
- complications specific to the pacemaker include a failure to pace, failure to sense, pulse generator failure, pacemaker syndrome and pacemaker mediated tachycardia

### Pacing Techniques
- temporary: transvenous (jugular, subclavian, femoral) or external (transcutaneous) pacing
- permanent: transvenous into RA, apex of RV, or both
- can sense and pace atrium, ventricle, or both
- new generation: rate responsive, able to respond to physiologic demand
- biventricular

**Systematic Review: Implantable Cardioverter Defibrillators for Adults with Left Ventricular Systolic Dysfunction**
Ann Intern Med 2007;147:251-262
**Study:** Meta-review of 12 RCTs used for ICD efficacy, 5 RCTs and 48 observational studies for effectiveness, and 21 RCTs and 43 observational studies for safety review.
**Population:** 8516 patients for ICD efficacy, 26,840 patients for effectiveness, and 86,809 patients for safety review with left ventricular ejection fraction ≤0.35.
**Intervention:** ICD implantation.
**Outcomes:** All-cause mortality and adverse events.
**Results:** ICDs reduced all-cause mortality by 20% (95% CI, 10%-29%; I2=44.4%) with greatest reduction (54%) in sudden cardiac death (CI 37%-63%; I2=0%). Observational studies had a reduced relative risk of 0.54 for all-cause mortality versus RCTs (CI 0.43-0.58, I2=60.4%). Rates of success of ICD implantation were 99% (CI 98.8%-99.3%) with a 1.2% (CI 0.9%-1.5%) chance of peri-implantation death. Post-implantation complications (per 100 patient yr) were: 1.4 (CI 1.2-1.6) device malfunctions; 1.5 (CI 1.3-1.8) lead problems; 0.6 (CI 0.5-0.8) implant site infection and 19.1 (CI 16.5-22.0) inappropriate discharges in RCTs versus a rate of 4.9 (CI 4.5-5.3) inappropriate discharges in observational studies.
**Conclusion:** ICDs are safe and effective in reducing mortality in adult patients with LV systolic dysfunction but carry significant risks of inappropriate discharges. Differences between RCTs and observational studies show that improved risk stratification of patients may further improve outcomes and reduce adverse events.

# Implantable Cardioverter Defibrillators

- sudden cardiac death (SCD) usually results from ventricular fibrillation (VFib), sometimes preceded by monomorphic or polymorphic ventricular tachycardia (VT)
- ICDs detect ventricular tachyarrhythmias and are highly effective in terminating VT/VFib and in aborting SCD
- mortality benefit vs. antiarrhythmics in secondary prevention
- benefit seen in patients with ischemic and non-ischemic cardiomyopathy, depressed left ventricular ejection fraction (LVEF), prolonged QRS
- see *Heart Failure*, C34 for current treatment recommendations

# Catheter Ablation

### Techniques

- radiofrequency (RF) ablation: a low-voltage high-frequency form of electrical energy (similar to cautery); RF ablation produces small, homogeneous, necrotic lesions approximately 5-7 mm in diameter and 3-5 mm in depth
- cryoablation: new technology which uses a probe with a tip that can decrease in temperature to -20˚C and -70˚C which produces small, necrotic lesions similar to RF ablation; when brought to -20˚C, the catheter tip reversibly freezes the area; bringing the tip down to -70˚C for 5 min permanently scars the tissue
  - advantage: can "test" areas before committing to an ablation
  - disadvantage: takes much longer than RF (5 min per cryoablation vs. 1 min per RF ablation)

### Indications

- paroxysmal SVT
  - AVNRT: accounts for more than half of all cases
- accessory pathway (orthodromic reciprocating tachycardia): 30% of SVT
  - re-entrant rhythm, with an accessory AV connection as the retrograde limb
  - corrected by targeting the accessory pathway
- atrial flutter: re-entry pathway in right atrium
- AFib: primarily pulmonary vein isolation, sometimes with added ablation in the atrial chambers
- ventricular tachycardia: focus arises from the right ventricular outflow tract and less commonly originates in the inferoseptal left ventricle near the apex (note: majority of cases of VT are due to scarring from previous MI and cannot be ablated)

### Major Complications

- 1% of patients; death: 0.1-0.2%
- cardiac: high grade AV block requiring permanent pacemaker (less risk with cryoablation), tamponade, pericarditis
- vascular: hematoma, vascular injury, thromboembolism, TIA/stroke
- pulmonary: pulmonary embolism

**Catheter Ablation for Atrial Fibrillation with Heart Failure (CASTLE-AF Trial)**
NEJM 2018;378:417-427
**Study**: Multicentre, open-label, randomized, controlled trial.
**Population**: 363 patients with symptomatic paroxysmal or persistent AF; New York Heart Association class II, III, or IV HF; a left ventricular ejection fraction of ≤35 percent; failure or unwillingness to take antiarrhythmic drug therapy.
**Intervention**: catheter ablation vs. medical therapy.
**Outcomes**: primary endpoint was a composite of death from any cause or worsening of heart failure that led to an unplanned overnight hospitalization. Major secondary endpoints were death from any cause, unplanned hospitalization related to heart failure, death from cardiovascular disease, cerebrovascular accident, unplanned hospitalization for cardiovascular disease, and any hospitalization. In the ablation group, procedure-related adverse events and atrial fibrillation-free intervals were also assessed
**Results**: After a median follow-up of 37.8 mo, the primary composite endpoint occurred in significantly fewer patients in the ablation group than in the medical-therapy group (28.5% vs. 44.6%; P=0.007). Significantly fewer patients in the ablation group died from any cause (13.4% vs. 25.0%; hazard ratio, 0.53; P=0.01), were hospitalized for worsening heart failure (20.7% vs. 66 35.9%; P=0.004), or died from cardiovascular causes (11.2% vs. 41 22.3%; P=0.009).
**Conclusions**: Catheter ablation for atrial fibrillation in patients with heart failure was associated with a significantly lower rate of a composite end point of death from any cause or hospitalization for worsening heart failure than was medical therapy.

# Ischemic Heart Disease

### Epidemiology

- most common cause of cardiovascular morbidity and mortality
- atherosclerosis and thrombosis are the most important pathogenetic mechanisms
- M:F = 2:1 with all age groups included (Framingham study), 8:1 for age <40, 1:1 for age >70
  - CHD incidence in women triples shortly after menopause
- peak incidence of symptomatic IHD is age 50-60 (men) and 60-70 (women)
- for primary prevention of ischemic heart disease see Family Medicine, FM7

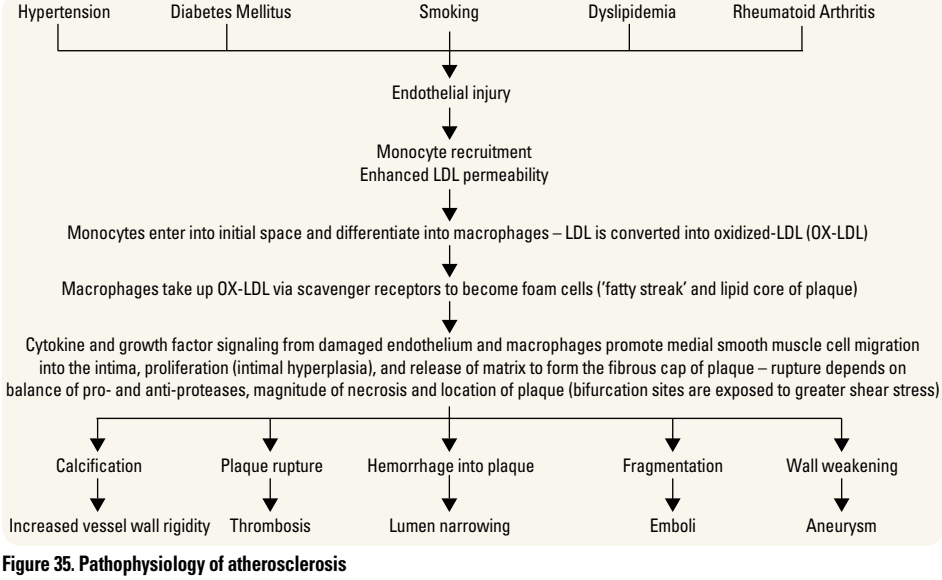



**Figure 35. Pathophysiology of atherosclerosis**

**Table 7. Risk Factors and Markers for Atherosclerotic Heart Disease**

| Non-Modifiable Risk Factors | Modifiable Risk Factors § | Markers of Disease |
|---|---|---|
| Age<br>Male, postmenopausal female<br>Family history (FHx) of MI*<br>First degree male relative <55<br>First degree female relative <65 | Hyperlipidemia*<br>HTN*<br>DM*<br>Cigarette smoking*<br>Psychosocial stress<br>Abdominal obesity<br>Sedentary lifestyle<br>Heavy alcohol intake<br>Not consuming fruits and vegetables daily<br>Elevated lipoprotein(a)<br>Hyperhomocysteinemia | Elevated high-sensitivity C-reactive protein (hsCRP)<br>Coronary artery calcification<br>Carotid IMT/plaque<br>Ankle-brachial index |

* Major risk factors
§ Modifiable risk factors account for >90% of MIs

# Chronic Stable Angina

## Definition
- symptom complex resulting from an imbalance between oxygen supply and demand in the myocardium

## Etiology and Pathophysiology
- factors that decrease myocardial oxygen supply:
  - decreased luminal diameter: atherosclerosis, vasospasm
  - decreased duration of diastole: tachycardia (decreased duration of diastolic coronary perfusion)
  - decreased hemoglobin: anemia
  - decreased $SaO_2$: hypoxemia
  - congenital anomalies
- factors that increase myocardial oxygen demand:
  - increased heart rate: hyperthyroidism
  - increased contractility: hyperthyroidism
  - increased wall stress: myocardial hypertrophy, aortic stenosis

## Signs and Symptoms
- typical
  1. retrosternal chest pain, tightness or discomfort radiating to left (± right) shoulder/arm/neck/jaw, associated with diaphoresis, nausea, anxiety
  2. predictably precipitated by the "3 Es": exertion, emotion, eating
  3. brief duration, lasting <10-15 min and typically relieved by rest and nitrates
- atypical/probable angina (meets 2 of the above)
- non-cardiac chest pain (meets none or 1 of the above)
- Levine's sign: clutching fist over sternum when describing chest pain
- anginal equivalents: dyspnea, acute LV failure, flash pulmonary edema

## Clinical Assessment
- history including directed risk factor assessment and physical exam
- labs: Hb, fasting glucose, fasting lipid profile
- ECG (at rest and during episode of chest pain if possible)
- CXR (suspected heart failure, valvular disease, pericardial disease, aortic dissection/aneurysm, or signs or symptoms of pulmonary disease)
- stress testing (see *Stress Testing*, C13) or angiography
- echo
- to assess systolic murmur suggestive of aortic stenosis, mitral regurgitation, and/or HCM
- to assess LV function in patients with Hx of prior MI, pathological Q waves, signs or symptoms of CHF

## Differential Diagnosis
- see *Differential Diagnosis of Common Presentations*, C4

## Treatment of Chronic Stable Angina
**1. General Measures**
- goals: to reduce myocardial oxygen demand and/or increase oxygen supply
- lifestyle modification (diet, exercise)
- treatment of risk factors: e.g. statins (see Endocrinology, E5, Family Medicine, FM9 for target lipid guidelines), antihypertensives
- pharmacological therapy to stabilize the coronary plaque to prevent rupture and thrombosis

**2. Antiplatelet Therapy (first-line therapy)**
- ASA
- clopidogrel when ASA absolutely contraindicated

**3. β-blockers (first-line therapy – improve survival in patients with hypertension)**
- increase coronary perfusion and decrease demand (HR, contractility) and BP (afterload)
- cardioselective agents preferred (e.g. metoprolol, atenolol) to avoid peripheral effects (inhibition of vasodilation and bronchodilation via β2 receptors)
- avoid intrinsic sympathomimetics (e.g. acebutolol) which increase demand



Chronic stable angina is most often due to a fixed stenosis caused by an atheroma

Acute coronary syndromes are the result of plaque rupture



**Canadian Cardiovascular Society (CCS) Functional Classification of Angina**
- **Class I:** ordinary physical activity (walking, climbing stairs) does not cause angina; angina with strenuous, rapid, or prolonged activity
- **Class II:** slight limitation of ordinary activity: angina brought on at >2 blocks on level or climbing >1 flight of stairs or by emotional stress
- **Class III:** marked limitation of ordinary activity: angina brought on at <2 blocks on level or climbing <1 flight of stairs
- **Class IV:** inability to carry out any physical activity without discomfort; angina may be present at rest

**4. Nitrates (symptomatic control, no clear impact on survival)**
- decrease preload (venous dilatation) and afterload (arteriolar dilatation), and increase coronary perfusion
- maintain daily nitrate-free intervals to prevent tolerance (tachyphylaxis)

**5. Calcium Channel Blockers (CCBs, second-line or combination)**
- increase coronary perfusion and decrease demand (HR, contractility) and BP (afterload)
- caution: verapamil/diltiazem combined with β-blockers may cause symptomatic sinus bradycardia or AV block

**6. ACE Inhibitors (ACEI, not used to treat symptomatic angina)**
- angina patients tend to have risk factors for CV disease which warrant use of an ACEI (e.g. HTN, DM, proteinuric renal disease, previous MI with LV dysfunction)
- benefit in all patients at high risk for CV disease (concomitant DM, renal dysfunction, or LV systolic dysfunction)

**7. Invasive Strategies**
- revascularization (see *Coronary Revascularization*, C31 and COURAGE trial sidebar)

### VARIANT ANGINA (PRINZMETAL'S ANGINA)
- myocardial ischemia secondary to coronary artery vasospasm, with or without atherosclerosis
- uncommonly associated with infarction or LV dysfunction
- typically occurs between midnight and 8 am, unrelated to exercise, relieved by nitrates
- typically ST elevation on ECG
- diagnosed by provocative testing with ergot vasoconstrictors (rarely done)
- treat with nitrates and CCBs

### SYNDROME X
- typical symptoms of angina but normal angiogram
- may show definite signs of ischemia with exercise testing
- thought to be due to inadequate vasodilator reserve of coronary resistance vessels
- better prognosis than overt epicardial atherosclerosis

**Optimal Medical Therapy with or without PCI for Stable Coronary Disease. COURAGE Trial**
NEJM 2007;356:1503-1516
**Study:** Randomized, controlled trial with median follow-up of 4.6 yr.
**Population:** 2287 patients who had objective evidence of myocardial ischemia and significant stable coronary artery disease.
**Intervention**: Patients were randomized to receive intensive pharmacologic therapy and lifestyle intervention with or without percutaneous coronary intervention (PCI).
**Outcome:** Primary outcome was all-cause mortality and nonfatal myocardial infarction (MI). Secondary outcome had additional events of stroke, all MI, and hospitalization for unstable angina with negative biomarkers.
**Results:** There was no significant difference in primary (unadjusted hazard ratio: 1.05; p=0.62) or secondary outcomes (hazard ratio: 1.05; p=0.62) between the PCI and non-PCI intervention groups. The PCI group had significantly lower rates of subsequent revascularization at 4.6 yr of follow-up (hazard ratio 0.60, p<0.001) and was more angina-free in the first 4 yr of follow-up.
**Conclusions:** PCI as an adjunct in initial management in patients with significant stable coronary artery disease does not reduce mortality, MI, stroke, or hospitalization for ACS, but does provide angina relief and reduced risk of revascularization.

## Acute Coronary Syndromes

### Definition
- ACS includes the spectrum of unstable angina (UA), NSTEMI, and STEMI; this distinction aids in providing the appropriate therapeutic intervention
  - **UA** is clinically defined by any of the following:
    - accelerating pattern of pain: increased frequency, increased duration, decreased threshold of exertion, decreased response to treatment
    - angina at rest
    - new-onset angina
    - angina post-MI or post-procedure (e.g. percutaneous coronary intervention [PCI], coronary artery bypass grafting [CABG])
  - **MI** (STEMI/NSTEMI) is defined by evidence of myocardial necrosis and is diagnosed by a rise/fall of serum markers plus any one of:
    - symptoms of ischemia (chest/upper extremity/mandibular/epigastric discomfort; dyspnea)
    - ECG changes (ST-T changes, new BBB or pathological Q waves)
    - imaging evidence (myocardial loss of viability, wall motion abnormality, or intracoronary thrombus)
    - if biomarker changes are unattainable, cardiac symptoms combined with new ECG changes is sufficient
  - **NSTEMI** meets criteria for MI without ST elevation or BBB
  - **STEMI** meets criteria for MI characterized by ST elevation or new BBB

### Investigations
- history and physical
  - note that up to 30% of MIs are unrecognized or "silent" due to atypical symptoms – more common in women, DM, elderly, post-heart transplant (because of denervation)
- ECG
- CXR
- labs
  - serum cardiac biomarkers for myocardial damage (repeat 8 h later) (see *Cardiac Biomarkers*, C11)
  - CBC, INR/PTT, electrolytes and magnesium, creatinine, urea, glucose, serum lipids
  - draw serum lipids within 24-48 h because values are unreliable from 2-48 d post-MI

### MANAGEMENT OF ACUTE CORONARY SYNDROMES

**1. General Measures**
- ABCs: assess and correct hemodynamic status first
- bed rest, cardiac monitoring, oxygen
- nitroglycerin SL followed by IV
- morphine IV

**2. Anti-Platelet and Anticoagulation Therapy**

- see also *CCS Antiplatelet Guidelines 2012* for details (free mobile apps available on iOS and Android platforms in the CCS app stores)
- ASA chewed
- NSTEMI
  - ticagrelor in addition to ASA or if ASA contraindicated, subcutaneous low molecular weight heparin or IV unfractionated heparin (UFH)
    - LMWH preferable, except in renal failure or if CABG is planned within 24 h
  - clopidogrel used if patient ineligible for ticagrelor
- if PCI is planned: ticagrelor or prasugrel and consider IV GP IIb/IIIa inhibitor (e.g. abciximab)
  - clopidogrel used if patient ineligible for ticagrelor and prasugrel
  - prasugel contraindicated in those with a history of stroke/TIA, and avoidance of or lower dose is recommended for those >75 yr old or weighing under 60 kg (TRITON-TIMI 38)
- anticoagulation options depend on reperfusion strategy:
  - primary PCI: UFH during procedure; bivalirudin is a possible alternative
  - thrombolysis: LMWH (enoxaparin) until discharge from hospital; can use UFH as alternative because of possible rescue PCI
  - no reperfusion: LMWH (enoxaparin) until discharge from hospital
- continue LMWH or UFH followed by oral anticoagulation at discharge if at high risk for thromboembolic event (large anterior MI, AFib, severe LV dysfunction, CHF, previous DVT or PE, or echo evidence of mural thrombus)

**3. β-blockers**

- STEMI: contraindications include signs of heart failure, low output states, risk of cardiogenic shock, heart block, asthma or airway disease; initiate orally within 24 h of diagnosis when indicated
- if β-blockers are contraindicated or if β-blockers/nitrates fail to relieve ischemia, non-dihydropyridine calcium channel blockers (e.g. diltiazem, verapamil) may be used as second-line therapy in the absence of severe LV dysfunction or pulmonary vascular congestion (calcium channel blockers do not prevent MI or decrease mortality)

**4. Invasive Strategies and Reperfusion Options**

- UA/NSTEMI: early coronary angiography ± revascularization if possible is recommended with any of the following high-risk indicators:
  - recurrent angina/ischemia at rest despite intensive anti-ischemic therapy
  - CHF or LV dysfunction
  - hemodynamic instability
  - high (≥3) TIMI risk score (tool used to estimate mortality following an ACS)
  - sustained ventricular tachycardia
  - dynamic ECG changes
  - high-risk findings on non-invasive stress testing
  - PCI within the previous 6 mo
  - repeated presentations for ACS despite treatment and without evidence of ongoing ischemia or high risk features
  - note: thrombolysis is NOT administered for UA/NSTEMI
- STEMI
  - after diagnosis of STEMI is made, do not wait for results of further investigations before implementing reperfusion therapy
  - goal is to re-perfuse artery: thrombolysis ("EMS-to-needle") within 30 min or primary PCI ("EMS-to-balloon") within 90 min (if available)
  - thrombolysis
    - preferred if patient presents ≤12 h of symptom onset, and <30 min after presentation to hospital, has contraindications to PCI, or PCI cannot be administered within 90 min
  - PCI
    - early PCI (≤12 h after symptom onset and <90 min after presentation) improves mortality vs. thrombolysis with fewer intra-cranial hemorrhages and recurrent MIs
    - primary PCI: without prior thrombolytic therapy – method of choice for reperfusion in experienced centres
    - rescue PCI: following failed thrombolytic therapy (diagnosed when following thrombolysis, ST segment elevation fails to resolve below half its initial magnitude and patient still having chest pain)



**TIMI Risk Score for UA/NSTEMI**

| Characteristics | Points |
|---|---|
| **Historical** | |
| Age ≥65 yr | 1 |
| ≥3 risk factors for CAD | 1 |
| Known CAD (stenosis ≥50%) | 1 |
| Aspirin® use in past 7 d | 1 |
| **Presentation** | |
| Recent (≤24 h) severe angina | 1 |
| ST-segment deviation ≥0.5 mm | 1 |
| Increased cardiac markers | 1 |

Risk Score = Total Points
If TIMI risk score ≥3, consider early LMWH and angiography
TIMI = thrombolysis in myocardial infarction
UA = unstable angina
JAMA 2000;284:835-842



Newer, more accurate risk quantification scores for UA/NSTEMI exist, such as the GRACE Risk Score; however, TIMI is still used most often

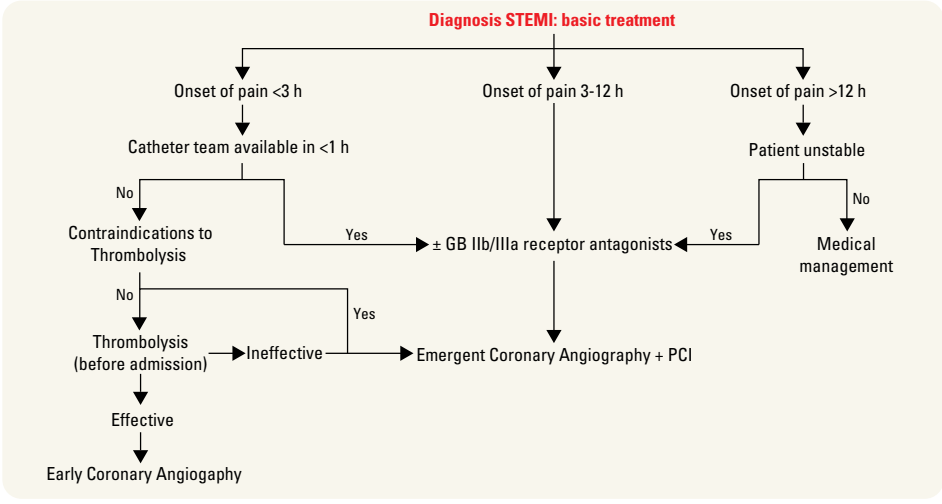



**Figure 36. Reperfusion strategy in STEMI**

**Table 8. Contraindications for Thrombolysis in STEMI**

| Absolute | Relative |
|---|---|
| Prior intracranial hemorrhage | Chronic, severe, poorly controlled HTN |
| Known structural cerebral vascular lesion | Uncontrolled HTN (sBP >180, dBP >110) |
| Known malignant intracranial neoplasm | Current anticoagulation |
| Significant closed-head or facial trauma (≤3 mo) | Noncompressible vascular punctures |
| Ischemic stroke (≤3 mo) | Ischemic stroke (≥3 mo) |
| Active bleeding | Recent internal bleeding (≤2-4 wk) |
| Suspected aortic dissection | Prolonged CPR or major surgery (≤3 wk) |
| | Pregnancy |
| | Active peptic ulcer disease |

## Long-Term Management of ACS

- risk of progression to MI or recurrence of MI or death is highest within 1 mo
- at 1-3 mo after the acute phase, most patients resume a clinical course similar to that in patients with chronic stable coronary disease
- pre-discharge workup: ECG and echo to assess residual LV systolic function
- drugs required in hospital to control ischemia should be continued after discharge in all patients
- other medications for long-term management of ACS are summarized below

**1. General Measures**
- education
- risk factor modification

**2. Antiplatelet and Anticoagulation Therapy**
- see also *CCS Antiplatelet Guidelines 2012* for details (free mobile apps available on iOS and Android platforms in the CCS app stores)
- ECASA 81 mg daily
- ticagrelor 90 mg twice daily or prasugrel 10 mg daily (at least 1 mo, up to 9-12 mo, if stent placed at least 12 mo)
- clopidogrel 75 mg daily can be used as alternatives to ticagrelor and prasugrel when indicated
- ± warfarin x 3 mo if high risk (large anterior MI, LV thrombus, LVEF <30%, history of VTE, chronic AFib)

**3. β-Blockers** (e.g. metoprolol 25-50 mg bid or atenolol 50-100 mg daily)

**4. Nitrates**
- alleviate ischemia but do not improve outcome
- use with caution in right-sided MI patients who have become preload dependent

**5. Calcium Channel Blockers** (NOT recommended as first line treatment, consider as alternative to β-blockers)

**6. Angiotensin-Converting Enzyme Inhibitors**
- prevent adverse ventricular remodelling
- recommended for asymptomatic high-risk patients (e.g. diabetics), even if LVEF >40%
- recommended for symptomatic CHF, reduced LVEF (<40%), anterior MI
- use ARBs in patients who are intolerant of ACEI; avoid combining ACEI and ARB

**7. ± Aldosterone Antagonists**
- if on ACEI and β-blockers and LVEF <40% and CHF or DM
- significant mortality benefit shown with eplerenone by 30 d

**8. Statins** (early, intensive, irrespective of cholesterol level; e.g. atorvastatin 80 mg daily)

**9. Invasive Cardiac Catheterization if indicated** (risk stratification)

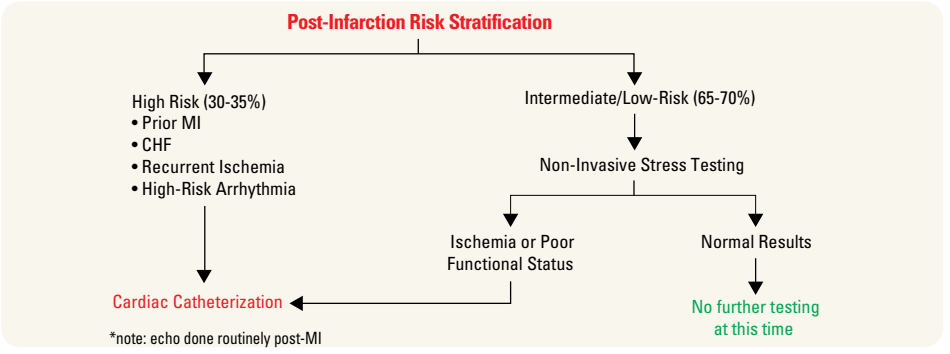



**Figure 37. Post-MI risk stratification**

## Prognosis following STEMI

- 5-15% of hospitalized patients will die
  - risk factors
    - infarct size/severity
    - age
    - comorbid conditions
    - development of heart failure or hypotension
- post-discharge mortality rates
  - 6-8% within first year, half of these within first 3 mo
  - 4% per year following first yr
  - risk factors
    - LV dysfunction
    - residual myocardial ischemia
    - ventricular arrhythmias
    - history of prior MI

**Table 9. Complications of Myocardial Infarction**

| Complication | Etiology | Presentation | Therapy |
|---|---|---|---|
| Arrhythmia | | | See *Arrhythmias*, C16 |
| 1. Tachycardia | Sinus, AFib, VT, VFib | First 48 h | |
| 2. Bradycardia | Sinus, AV block | First 48 h | |
| Myocardial Rupture | | | |
| 1. LV free wall | Transmural infarction | 1-7 d | Surgery |
| 2. Papillary muscle (→ MR) | Inferior infarction | 1-7 d | Surgery |
| 3. Ventricular septum (→ VSD) | Septal infarction | 1-7 d | Surgery |
| Shock/CHF | Infarction or aneurysm | Within 48 h | Inotropes, intra-aortic balloon pump |
| Post-Infarct Angina | Persistent coronary stenosis<br>Multivessel disease | Anytime | Aggressive medical therapy<br>PCI or CABG |
| Recurrent MI | Reocclusion | Anytime | Aggressive medical therapy<br>PCI or CABG |
| Thromboembolism | Mural/apical thrombus<br>DVT | 7-10 d, up to 6 mo | Anticoagulation |
| Pericarditis | Inflammatory | 1-7 d | ASA |
| Dressler's Syndrome | Autoimmune | 2-8 wk | |

**Is this Patient Having a Myocardial Infarction? From The Rational Clinical Examination**
JAMA 2009; http://www.jamaevidence.com/content/3484335
**Study:** Systematic review of articles assessing the accuracy and precision of the clinical exam in the diagnosis of an acute myocardial infarction.
**Results:** In patients with normal or non-diagnostic ECG, no established CAD, and prolonged or recurrent chest pain typical of their usual discomfort, radiation of pain to the shoulder OR both arms had the highest positive likelihood ratio (+LR) of 4.1 (95% CI 2.5-6.5) and a negative likelihood ratio (-LR) of 0.68 (95% CI 0.52-0.89). Radiation to right arm had a +LR of 3.8 (95% CI 2.2-6.6) and –LR of 0.86 (95% CI 0.77-0.96), vomiting had a +LR of 3.5 (95% CI 2.0-6.2) and –LR of 0.87 (95% CI 0.79-0.97), while radiation to left arm only had a +LR of 1.3 (95% CI 0.93-1.8) and a –LR of 0.9 (95% CI 0.76-1.1).
**Conclusions:** The most compelling features that increase likelihood of an MI are ST-segment and cardiac enzyme elevation, new Q-wave, and presence of an S3 heart sound. In patients where the diagnosis of MI is uncertain, radiation of pain to the shoulder OR both arms, radiation to the right arm, and vomiting had the best predictive values, while radiation to the left arm is relatively non-diagnostic.

**Complications of MI**

**CRASH PAD**
**C**ardiac **R**upture
**A**rrhythmia
**S**hock
**H**ypertension/Heart failure
**P**ericarditis/Pulmonary emboli
**A**neurysm
**D**VT

Resting LVEF is a useful prognostic factor

**Enoxaparin vs. Unfractionated Heparin with Fibrinolysis for ST-elevation Myocardial Infarction**
NEJM 2006;354:1477-1488
**Study:** Prospective multicentre RCT.
**Patients:** 20,479 patients (median age 60 yr, 77% male) with STEMI who were scheduled to undergo fibrinolysis.
**Intervention:** Patients were randomized to receive either enoxaparin or weight based unfractionated heparin in addition to thrombolysis and standard therapies.
**Primary Outcome:** Death or recurrent nonfatal MI 30 d post-event.
**Results:** The composite primary outcome occurred less often in the enoxaparin group compared with those who received unfractionated heparin (9.9% vs. 12.0%, p<0.001, NNT=47). Taken separately, there was a trend toward reduced mortality (6.9% vs. 7.5%, p=0.11) and a significant reduction in nonfatal reinfarction (3.0% vs. 4.5%, p<0.001) in the enoxaparin group. The risk of major bleeding was significantly increased in the enoxaparin group (2.1% vs. 1.4%, p<0.001, NNH=142).
**Conclusion:** In patients with STEMI receiving thrombolysis, enoxaparin is superior to unfractionated heparin in preventing recurrent nonfatal MI and may lead to a small reduction in mortality.

# Treatment Algorithm for Chest Pain

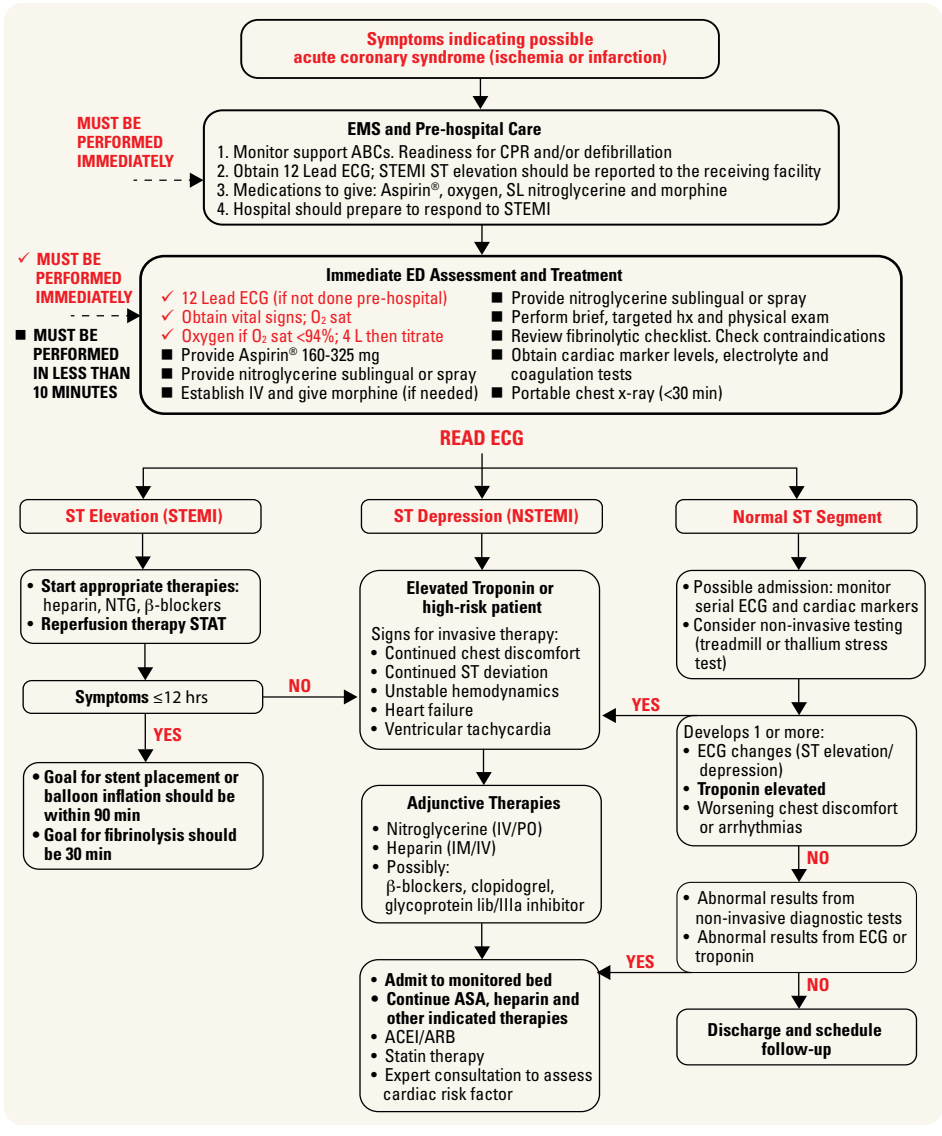



**Figure 38. AHA ACLS acute coronary syndrome algorithm**
Adapted from: Jeffery Media Productions 2016. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes. Circulation. 2014 Jan 1:CIR-0000000000000134

**Intensive vs. Moderate Lipid Lowering with Statins after Acute Coronary Syndromes**
NEJM 2004;350:1495-1504
**Study:** Prospective, double blind, RCT; mean follow-up of 2 yr.
**Population:** 4162 patients who had been hospitalized for an ACS within the preceding 10 d.
**Intervention:** Patients were randomized to receiving pravastatin 40 mg or atorvastatin 80 mg daily.
**Primary Outcome:** Composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 d after randomization), and stroke.
**Results:** High dose atorvastatin was associated with a 16% hazard ratio reduction (p=0.005; 95% CI 5-26%) in the primary outcome compared to standard dose pravastatin.
**Conclusions:** In patients who recently experienced an ACS, high dose statin therapy provides greater protection against death and major cardiovascular events than standard dose therapy.

# Coronary Revascularization

## PERCUTANEOUS CORONARY INTERVENTION

- interventional cardiology technique aimed at relieving significant coronary stenosis
- main techniques: balloon angioplasty, stenting
- less common techniques: rotational/directional/extraction atherectomy

### Indications

- medically refractory angina
- NSTEMI/UA with high risk features (e.g. high TIMI risk score)
- primary/rescue PCI for STEMI

### Balloon Angioplasty and Intracoronary Stenting

- coronary lesions dilated with balloon inflation
- major complication is restenosis (approximately 15% at 6 mo), felt to be due to elastic recoil and neointimal hyperplasia
- majority of patients receive intracoronary stent(s) to prevent restenosis
  - bare metal stent (BMS) versus drug-eluting stents: PRAMI trial demonstrated stenting non-culprit lesions results in 14% absolute risk reduction of cardiac death, nonfatal MI, or refractory angina
  - coated with antiproliferative drugs (sirolimus, paclitaxel, everolimus)
  - reduced rate of neointimal hyperplasia and restenosis compared to BMS (5% vs. 20%)
  - complication: late stent thrombosis (5 events per 1000 stents implanted)

**Treatment of NSTEMI**

**BEMOAN**
β-blocker
**E**noxaparin
**M**orphine
**O**$_2$
**A**SA
**N**itrates

### Adjunctive Therapies
- ASA and heparin decrease post-procedural complications
- further reduction in ischemic complications has been demonstrated using GPIIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban) in coronary angiography and stenting
- following stent implantation
  - dual antiplatelet therapy (ASA and clopidogrel) for 1 mo with BMS or ≥12 mo with DES
  - DAPT study showed benefit of dual antiplatelet therapy beyond 12 mo
  - ASA and prasugrel can be considered for those at increased risk of stent thrombosis

### Procedural Complications
- mortality and emergency bypass rates <1%
- nonfatal MI: approximately 2-3%

## CORONARY ARTERY BYPASS GRAFT SURGERY
- objective of CABG is complete reperfusion of the myocardium

### Indications
- CABG
  - ≥50% diameter stenosis in the left main coronary artery
  - ≥70% diameter stenosis in three major coronary arteries
  - ≥70% diameter stenosis in the proximal LAD artery plus one other major coronary artery
  - survivors of sudden cardiac arrest with presumed ischemia-mediated VT caused by significant (≥70% diameter) stenosis in a major coronary artery
- other
  - ≥70% diameter stenosis in two major coronary arteries (without proximal LAD disease) and evidence of extensive ischemia
  - ≥70% diameter stenosis in the proximal LAD artery and evidence of extensive ischemia
  - multivessel CAD in patients with diabetes
  - LV systolic dysfunction (LVEF 35% to 50%) and significant multivessel CAD or proximal LAD stenosis where viable myocardium is present in the region of intended revascularization
- PCI
  - UA/NSTEMI if not a CABG candidate
  - STEMI when PCI can be performed more rapidly and safely than CABG
- CABG or PCI
  - one or more significant (≥70% diameter) coronary artery stenosis amenable to revascularization and unacceptable angina despite medical therapy

**Duration of Triple Therapy in Patients Required Oral Anticoagulation (OAC) After Drug-Eluting Stent Implantation: The ISAR-TRIPLE Trial.**
Journal of the American College of Cardiology 66.9 (2015):1088-1089
**Study**: RCT comparing whether shortening the duration of clopidogrel therapy from 6 mo to 6 wk after DES implantation was associated with superior net clinical outcome in patients receiving concomitant aspirin and OAC.
**Population**: 614 patients from 3 European centres receiving DES implantation on OAC and aspirin.
Intervention: 6 wk vs. 6 mo clopidogrel therapy post-DEC.
**Outcome**: Death, myocardial infarction, definite stent thrombosis, stroke, thrombolysis in myocardial infraction major bleeding at 9 mo
**Results**: Primary endpoint occurred in 9.8% in 6 wk group vs. 27 patients in 6 mo group (HR: 1.14; 95% CI: 0.68-1.91; p-0.63)
**Conclusions**: Six weeks of triple therapy is not superior to 6 mo. Physician should weigh trade-off between ischemic and bleeding risk when choosing shorter or longer duration of triple therapy.

**Table 10. Choice of Revascularization Procedure**

| | PCI | CABG |
|---|---|---|
| **Advantages** | Less invasive technique<br>Decreased periprocedural morbidity and mortality<br>Shorter periprocedural hospitalization | Greater ability to achieve complete revascularization<br>Decreased need for repeated revascularization procedures |
| **Indications** | Single or double-vessel disease<br>Inability to tolerate surgery | Triple-vessel or left main disease<br>DM<br>Plaque morphology unfavourable for PCI |

**Table 11. Conduits for CABG**

| Graft | Occlusion/Patency Rate | Considerations |
|---|---|---|
| **Saphenous Vein Grafts (SVG)** | At 10 yr, 50% occluded, 25% stenotic, 25% angiographically normal | Used when arterial grafts are not available or many grafts are required, such as triple or quadruple bypass |
| **Left Internal Thoracic/Mammary Artery (LITA/LIMA) (LIMA to LAD)** | 90-95% patency at 15 yr | Most preferred option because of excellent patency<br>Improved event-free survival (angina, MI)<br>Decreased late cardiac events<br>No increase in operative risk |
| **Right Internal Thoracic/ Mammary Artery (RITA/RIMA)** | Pedicled RIMA patency comparable to LIMA<br>Free RIMA patency less | Used in bilateral ITA/IMA grafting<br>Patients receiving bilateral ITAs/IMAs have less risk of recurrent angina, late MI, angioplasty |
| **Radial Artery (free graft)** | 85-90% patency at 5 yr | Prone to severe vasospasm post-operatively due to muscular wall |
| **Right Gastroepiploic Artery** | 80-90% patency at 5 yr | Primarily used as an in situ graft to bypass the RCA<br>Use limited because of the fragile quality of the artery, other technical issues, increased operative time (laparotomy incision), and incisional discomfort with associated ileus |
| **Complete Arterial Revascularization** | | For younger patients (<60 yr of age)<br>Is preferred due to longer term graft patency |
| **Redo Bypass Grafting** | | Operative mortality 2-3x higher than first operation<br>10% perioperative MI rate<br>Reoperation undertaken only in symptomatic patients who have failed medical therapy and in whom angiography has documented progression of the disease<br>Increased risk with redo-sternotomy secondary to adhesions which may result in laceration to aorta, RV, IMA/ITA, and other bypass grafts |

**Percutaneous Coronary Intervention vs. Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease: The SYNTAX Trial**
NEJM 2009;360;961-972
**Study:** Prospective RCT.
**Population:** 1800 patients with untreated three-vessel or left main coronary artery disease and anatomically equivalent for both Percutaneous Intervention (PCI) and Coronary Artery Bypass Graft (CABG).
**Intervention:** PCI vs. CABG.
**Outcome:** Composite of death from any cause, stroke, MI, or repeat revascularization in 12 mo post-intervention.
**Results:** Incidence of primary outcome was lower in the CABG intervention vs. PCI (12.4% vs. 17.8%, p=0.002, NNT=19). PCI was associated with significantly higher rates of repeat revascularization (13.5% vs. 5.9%, p<0.001) and cardiac death (3.7% vs. 2.1%, p=0.05), while CABG had higher rates of stroke (2.2% vs. 0.6%, p=0.03).
**Conclusions:** In patients with three-vessel or left main coronary artery disease CABG is superior to PCI in preventing major adverse cardiovascular and cerebrovascular events within 12 mo of intervention.

### Operative Issues
- left ventricular (LV) function is an important determinant of outcome of all heart diseases
- patients with severe LV dysfunction usually have poor prognosis, but surgery can sometimes dramatically improve LV function
- assess viability of non-functioning myocardial segments in patients with significant LV dysfunction using delayed thallium myocardial imaging, stress echocardiography, PET scanning, or MRI

### CABG and Antiplatelet Regimens
- refer to CCS guidelines – 2012 update on antiplatelet therapy – for more information
- prior to CABG, clopidogrel, and ticagrelor should be discontinued for 5 d and prasugrel for 7 d before surgery
- dual antiplatelet therapy should be continued for 12 mo in patients with ACS within 48-72 h after CABG
- ASA (81 mg) continued indefinitely (can be started 6 h after surgery)
- patients requiring CABG after PCI should continue their dual antiplatelet therapy as recommended in the post-PCI guidelines

**Table 12. Risk Factors for CABG Mortality and Morbidity (decreasing order of significance)**

| Risk Factors for CABG Mortality | Risk Factors for CABG Post-Operative Morbidity or Increased Length of Stay |
|---|---|
| Urgency of surgery (emergent or urgent) | Reoperation |
| Reoperation | Emergent procedure |
| Older age | Pre-operative intra-aortic balloon pump (IABP) |
| Poor left ventricular function (see below) | CHF |
| Female gender | CABG + valve surgery |
| Left main disease | Older age |
| Others include catastrophic conditions (cardiogenic shock, ventricular septal rupture, ongoing CPR), dialysis-dependent renal failure, end-stage COPD, DM, cerebrovascular disease, and peripheral vascular disease | Renal dysfunction<br>COPD<br>DM<br>Cerebrovascular disease |

**Safety and Efficacy of Drug-Eluting and Bare Metal Stents**
Circulation 2009;119;3198-3206
**Study:** Meta-analysis of RCTs and observational studies. 22 RCTs and 34 observational studies.
**Population:** 9470 and 182,901 patients in RCTs and observational studies respectively who underwent percutaneous coronary intervention.
**Intervention:** Drug-Eluting Stents (DES) versus Bare Metal Stents (BMS).
**Outcome:** All-cause mortality, myocardial infarction (MI), and target vessel revascularization (TVR).
**Results:** No difference in mortality was found between DES vs. BMS by RCTs, while observational studies showed significantly lower mortality rates in DES-treated patients (hazard ratio (HR) 0.78, p<0.001). No difference in MI incidence was found in RCTs, while lower incidences of MI were found in observational studies (HR 0.87, p=0.014). DES has a significantly lower TVR rate in both RCT (HR 0.45, p<0.001) and observational studies (HR 0.46, p<0.001).
**Conclusions:** DES significantly reduces rates of TVR compared to BMS. Although there is no difference in mortality or MI incidence as found by RCTs, observational studies suggest lowered mortality and MI rates in patients with DES over BMS.

### Procedural Complications
- CABG using cardiopulmonary bypass (CPB)
  - stroke and neurocognitive defects (microembolization of gaseous and particulate matter)
  - immunosuppression
  - systemic inflammatory response leading to:
    - myocardial dysfunction
    - renal dysfunction
    - neurological injury
    - respiratory dysfunction
    - coagulopathies

## OFF-PUMP CORONARY ARTERY BYPASS SURGERY

### Procedure
- avoids the use of CPB by allowing surgeons to operate on a beating heart
  - stabilization devices (e.g. Genzyme Immobilizer®) hold heart in place allowing operation while positioning devices (Medtronic Octopus® and Starfish® system) allow the surgeon to lift the beating heart to access the lateral and posterior vessels
  - procedure is safe and well tolerated by most patients; however, this surgery remains technically more demanding

### Indications/Contraindications
- used in poor candidates for CPB who have: calcified aorta, poor LVEF, severe peripheral vascular disease (PVD), severe COPD, chronic renal failure, coagulopathy, transfusion objections (e.g. Jehovah's Witness), good target vessels, anterior/lateral wall revascularization, target revascularization in older, sicker patients
- **absolute contraindications**: hemodynamic instability, poor quality target vessels including intramyocardial vessels, diffusely diseased vessels, and calcified coronary vessels
- **relative contraindications**: cardiomegaly/CHF, critical left main disease, small distal targets, recent or current acute MI, cardiogenic shock, LVEF <35%

### Outcomes
- off-pump coronary artery bypass (OPCAB) surgery decreases in-hospital morbidity (decreased incidence of chest infection, inotropic requirement, supraventricular arrhythmia), blood product transfusion, ICU stay, length of hospitalization, and CK-MB and troponin I levels
- no significant difference in terms of survival at 2 yr, frequency of cardiac events (MI, PCI, CHF, recurrent angina, redo CABG), or medication usage compared to on-pump CABG

# Heart Failure

- see also *CCS Heart Failure Guidelines 2012* for details (free mobile apps available on iOS and Android platforms in the CCS app stores) as well as the CCS Heart Failure Guidelines Compendium available at CCS.ca

## Congestive Heart Failure

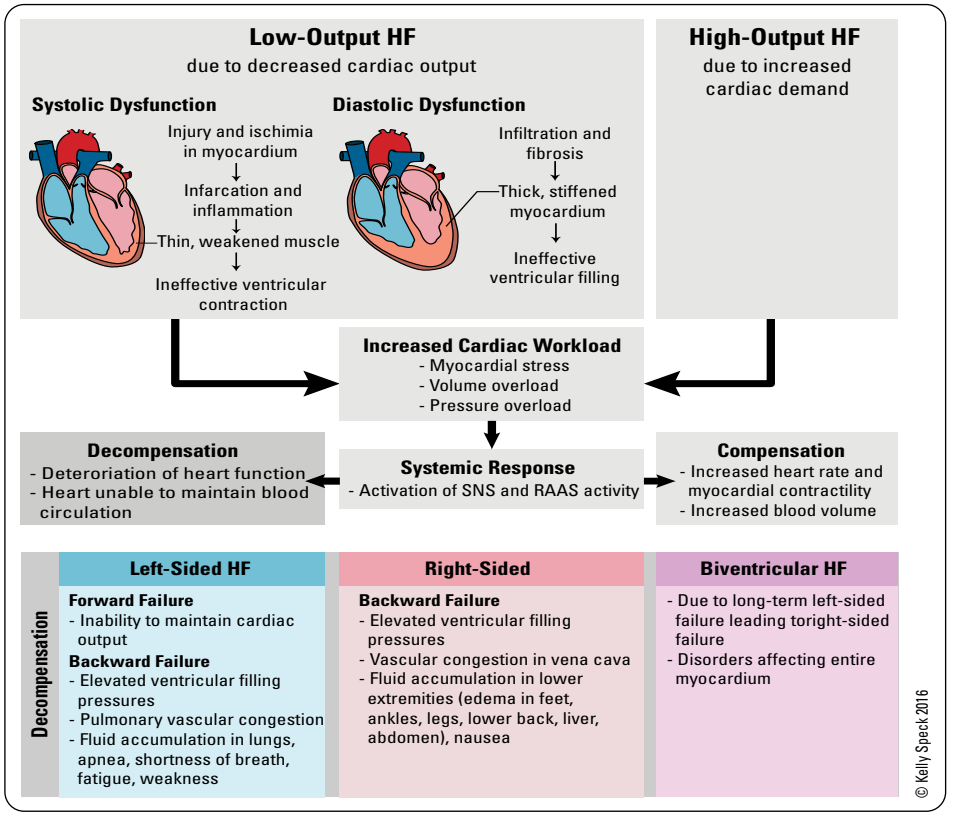



**Figure 39. Congestive heart failure**

**Table 13. Signs and Symptoms of Left vs. Right Heart Failure**

| | Left Failure | Right Failure |
|---|---|---|
| **Low Cardiac Output (Forward)** | Fatigue<br>Syncope<br>Systemic hypotension<br>Cool extremities<br>Slow capillary refill<br>Peripheral cyanosis<br>Pulsus alternans<br>Mitral regurgitation<br>S3 | Left failure symptoms if decreased RV output leads to LV underfilling<br>Tricuspid regurgitation<br>S3 (right-sided) |
| **Venous Congestion (Backward)** | Dyspnea, orthopnea, PND<br>Cough<br>Crackles | Peripheral edema<br>Elevated JVP with abdominojugular reflux, and ± Kussmaul's sign<br>Hepatomegaly<br>Pulsatile liver |

### Pathophysiology

- most common causes are ischemic heart disease, hypertension and valvular heart disease
- myocardial insult causes pump dysfunction/impaired filling leading to myocardial remodelling
  - pressure overload (e.g. AS or HTN) leads to compensatory hypertrophy (i.e. concentric remodelling) and eventually interstitial fibrosis
  - volume overload (e.g. aortic insufficiency) leads to dilatation (i.e. eccentric remodelling)
  - both processes lead to maladaptive changes contributing to disease process
- results in decreased volume cardiac output resulting in activation of the SNS and RAAS
- $Na^+$ and water retention, which increase preload and afterload, and tachycardia perpetuate the cycle of increasing cardiac demand and thus decompensation

**Does this Dyspneic Patient in the Emergency Department have Congestive Heart Failure?**
JAMA 2005;294:1944-1956

| | LR + (95% CI) | LR – (95% CI) |
|---|---|---|
| Initial clinical judgment | 4.4 (1.8-10.0) | 0.45 (0.28-0.73) |
| **Past Medical History** | | |
| Heart failure | 5.8 (4.1-8.0) | 0.45 (0.38-0.53) |
| Myocardial infarction | 3.1 (2.0-4.9) | 0.69 (0.58-0.82) |
| Coronary artery disease | 1.8 (1.1-2.8) | 0.68 (0.48-0.96) |
| **Symptoms** | | |
| Paroxysmal nocturnal dyspnea | 2.6 (1.5-4.5) | 0.7 (0.54-0.91) |
| Orthopnea | 2.2 (1.2-3.9) | 0.65 (0.45-0.92) |
| Dyspnea on exertion | 1.3 (1.2-1.4) | 0.48 (0.35-0.67) |
| **Physical Exam** | | |
| Third heart sound | 11 (4.9-25) | 0.88 (0.83-0.94) |
| Jugular venous distension | 5.1 (3.2-7.9) | 0.66 ( 0.57-0.77) |
| Rales | 2.8 (1.9-4.1) | 0.51 (0.37-0.70) |
| Lower extremity edema | 2.3 (1.5-3.7) | 0.64 (0.47-0.87) |
| **Chest Radiograph** | | |
| Pulmonary venous congestion | 12 (6.8-21) | 0.48 (0.28-0.83) |
| Interstitial edema | 12 (5.2-27) | 0.68 (0.54-0.85) |
| Cardiomegaly | 3.3 (2.4-4.7) | 0.33 (0.23-0.48) |
| **ECG** | | |
| Atrial fibrillation | 3.8 (1.7-8.8) | 0.79 (0.65-0.96) |
| Any abnormal finding | 2.2 (1.6-3.1) | 0.64 (0.47-0.88) |

**Dichotomies of Heart Failure**
- Forward vs. backward
- Left-sided vs. right-sided
- Systolic vs. diastolic dysfunction
- Low output vs. high output

**Use Ejection Fraction to Grade LV Dysfunction**
- Grade I (EF >60%) (Normal)
- Grade II (EF = 40-59%)
- Grade III (EF = 21-39%)
- Grade IV (EF ≤20%)

## Heart Failure with Reduced Ejection Fraction (HFREF: LVEF ≤40%)

- impaired myocardial contractile function → decreased LVEF and SV → decreased CO
- volume overload is the typical phenotype
- findings: apex beat displaced, S3, cardiothoracic ratio >0.5, decreased LVEF, LV dilatation
- causes
  - ischemic (e.g. extensive CAD, previous MI)
  - non-ischemic
    - HTN
    - DM
    - alcohol (and other toxins)
    - myocarditis
    - dilated cardiomyopathy (multiple causes – see *Dilated Cardiomyopathy*, C40)
    - tachycardia-induced

## Heart Failure with Mid-range Ejection Fraction (HF-mrEF: LVEF 41-49%)

- epidemiological studies are currently being conducted to better characterize clinical management of this group
- causes: strong association with CAD

## Heart Failure with Preserved Ejection Fraction (HFPEF: LVEF ≥50%)

- previously known as "diastolic heart failure"
- concentric remodelling with a "stiff" left ventricle is the typical phenotype
- 1/2 of patients with heart failure have preserved EF; confers similar prognosis to HFREF; more common in the elderly and females
- reduced LV compliance causes increased LV filling pressures, increased LA pressure/volume, and pulmonary congestion
- findings: HTN, apex beat sustained, S4, normal-sized heart on CXR, LVH on ECG/echo, normal EF
- causes
  - transient: ischemia (e.g. CAD, MI)
  - permanent: severe hypertrophy (HTN, aortic stenosis, HCM), restrictive cardiomyopathy (e.g. amyloid), MI

## High-Output Heart Failure

- caused by demand for increased cardiac output
- often exacerbates existing heart failure or decompensates a patient with other cardiac pathology
- differential diagnosis: anemia, thiamine deficiency (beriberi), hyperthyroidism, A-V fistula or L-R shunting, Paget's disease, renal disease, hepatic disease

## Precipitants of Symptomatic Exacerbations

- consider natural progression of disease vs. new precipitant
- always search for reversible cause
- differential diagnosis can also be organized as follows:
  - new cardiac insult/disease: MI, arrhythmia, valvular disease
  - new demand on CV system: HTN, anemia, thyrotoxicosis, infection
  - medication non-compliance
  - dietary indisretion e.g. salt intake
  - obstructive sleep apnea

## Investigations

- identify and assess precipitating factors and treatable causes of CHF
- blood work: CBC, electrolytes (including calcium and magnesium), BUN, creatinine, fasting blood glucose, HbA1c, lipid profile, liver function tests, serum TSH ± ferritin, BNP, uric acid
- ECG: look for chamber enlargement, arrhythmia, ischemia/infarction
- CXR: cardiomegaly, pleural effusion, redistribution, Kerley B lines, bronchiolar-alveolar cuffing
- echo: systolic function (LVEF), diastolic function (E/A ratio, E/e'), cardiac dimensions, wall motion abnormalities, right ventricular systolic pressure (from TR jet), valvular disease, pericardial effusion
- radionuclide angiography: LVEF
- myocardial perfusion scintigraphy (thallium or sestamibi SPECT)

## Acute Treatment of Pulmonary Edema

- treat acute precipitating factors (e.g. ischemia, arrhythmias)
- **L** – Lasix® (furosemide) 40-500 mg IV
- **M** – morphine 2-4 mg IV: decreases anxiety and preload (venodilation)
- **N** – nitroglycerin: topical/IV/SL - use with caution in preload-dependent patients (e.g. right HF or RV infarction) as it may precipitate CV collapse
- **O** – oxygen: in hypoxemic patients
- **P** – positive airway pressure (CPAP/BiPAP): decreases preload and need for ventilation when appropriate
- **P** – position: sit patient up with legs hanging down unless patient is hypotensive



**A Validated Clinical and Biochemical Score for the Diagnosis of Acute Heart Failure: the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Acute Heart Failure Score**
Am Heart J 2006;151:48-54

| Predictor | Possible Score |
|---|---|
| Age >75 yr | 1 |
| Orthopnea present | 2 |
| Lack of cough | 1 |
| Current loop diuretic use (before presentation) | 1 |
| Rales on lung exam | 1 |
| Lack of fever | 2 |
| Elevated NT-proBNP (>450 pg/mL if <50 yr, >900 pg/mL if >50 yr) | 4 |
| Interstitial edema on chest x-ray | 2 |
| Total | /14 |

Likelihood of heart failure
Low = 0-5
Intermediate = 6-8
High = 9-14

Brain natieuretic peptide (BNP) is secreted by ventricles due to LV stretch and wall tension. Cardiomyocytes secrete BNP precursor that is cleaved into proBNP. After secretion into ventricles, proBNP is cleaved into the active C-terminal portion and the inactive NT-proBNP. The above scoring algorithm developed by Baggish et al. is commonly used. A score of <6 has a negative predictive value of 98%, while scores ≥6 had a sensitivity of 96% and specificity of 84% (p<0.001) for the diagnosis of acute heart failure.



**New York Heart Association (NYHA) Functional Classification of Heart Failure**

- **Class I:** ordinary physical activity does not cause symptoms of HF
- **Class II:** comfortable at rest, ordinary physical activity results in symptoms
- **Class III:** marked limitation of ordinary activity; less than ordinary physical activity results in symptoms
- **Class IV:** inability to carry out any physical activity without discomfort; symptoms may be present at rest



**Five Most Common Causes of CHF**

- CAD (60-70%)
- HTN
- Idiopathic (often dilated cardiomyopathy)
- Valvular (e.g. AS, AR, and MR)
- Alcohol (dilated cardiomyopathy)



**Precipitants of Heart Failure**

**HEART FAILED**
**H**ypertension (common)
**E**ndocarditis/environment (e.g. heat wave)
**A**nemia
**R**heumatic heart disease and other valvular disease
**T**hyrotoxicosis
**F**ailure to take meds (very common)
**A**rrhythmia (common)
**I**nfection/Ischemia/Infarction (common)
**L**ung problems (PE, pneumonia, COPD)
**E**ndocrine (pheochromocytoma, hyperaldosteronism)
**D**ietary indiscretions (common)

- in ICU setting or failure of LMNOPP: other interventions may be necessary
  - nitroprusside IV
  - hydralazine PO
  - sympathomimetics
    - dopamine
      - low dose: selective renal vasodilation (high potency D1 agonist)
      - medium dose: inotropic support (medium potency β1 agonist)
      - high dose: increases SVR (low potency β1 agonist), which is undesirable
    - dobutamine
      - β1-selective agonist causing inotropy, tachycardia, hypotension (low dose) or hypertension (high dose); most serious side effect is arrhythmia, especially AF
    - phosphodiesterase inhibitors (milrinone)
      - inotropic effect and vascular smooth muscle relaxation (decreased SVR), similar to dobutamine
- consider pulmonary artery catheter to monitor pulmonary capillary wedge pressure (PCWP) if patient is unstable or a cardiac etiology is uncertain (PCWP >18 indicates likely cardiac etiology)
- mechanical ventilation as needed
- rarely used, but potentially life-saving measures:
  - intra-aortic balloon pump (IABP) - reduces afterload via systolic unloading and improves coronary perfusion via diastolic augmentation
  - left or right ventricular assist device (LVAD/RVAD)
  - cardiac transplant

## Long-Term Management

- overwhelming majority of evidence-based management applies to HFREF
- currently no proven pharmacologic therapies shown to reduce mortality in HFPEF; control risk factors for HFPEF (e.g. hypertension)

## Conservative Measures

- symptomatic measures: oxygen in hospital, bedrest, elevate the head of bed
- lifestyle measures: diet, exercise, DM control, smoking cessation, decrease alcohol consumption, patient education, sodium and fluid restriction
- multidisciplinary heart failure clinics: for management of individuals at higher risk, or with recent hospitalization

## Non-Pharmacological Management

- from CCS guidelines (2017 update)
- cardiac rehabilitation: participation in a structured exercise program for NYHA class I-III after clinical status assessment to improve quality of life (HF-ACTION trial)

## Pharmacological Therapy (* indicates initial therapy)

- **ACEI/ARB***: Renin-angiotensin-aldosterone blockade
  - ACEI: standard of care – slows progression of LV dysfunction and improves survival
    - all symptomatic patients functional class II-IV
    - all asymptomatic patients with LVEF <40%
    - post-MI
  - angiotensin II receptor blockers
    - second-line to ACEI (if ACEI not tolerated), or as adjunct to ACEI if β-blockers not tolerated
      - combination with ACEI is not routinely recommended and should be used with caution as it may precipitate hyperkalemia, renal failure, the need for dialysis (CHARM, ONTARGET)
    - combination angiotensin II receptor blockers with neprilysin inhibitors (ARNI) is a new class of medication that has morbidity and mortality benefit over ACEI alone; it has been recommended to replace ACEI or ARBs for patients who have persistent symptoms (PARADIGM HF)

- **β-blockers***: slow progression and improve survival
  - class I-III with LVEF <40%
  - stable class IV patients
  - carvedilol improves survival in class IV HF (COMET)
  - note: should be used cautiously, titrate slowly because may initially worsen CHF

- **Diuretics***: symptom control, management of fluid overload
  - furosemide (40-500 mg daily) for potent diuresis
  - metolazone may be used with furosemide to increase diuresis
  - furosemide, metolazone, and thiazides oppose the hyperkalemia that can be induced by β-blockers, ACEI, ARBs, and aldosterone antagonists

- **Mineralocorticoid receptor (aldosterone) antagonists**: mortality benefit in symptomatic heart failure and severely depressed ejection fraction
  - spironolactone or eplerenone – for symptomatic heart failure in patients already on ACEI, β-blocker and loop diuretic
  - note: potential for life threatening hyperkalemia
    - monitor $K^+$ after initiation and avoid if Cr >220 μmol/L or $K^+$ >5.2 mmol/L

- **Digoxin and cardiac glycosides**: digoxin improves symptoms and decreases hospitalizations; no effect on mortality
  - indications: patient in sinus rhythm and symptomatic on ACEI or CHF and AFib
  - patients on digitalis glycosides may worsen if these are withdrawn



The most common cause of right heart failure is left heart failure



**Measuring NT-Pro BNP**

BNP is secreted by ventricles due to LV stretch and wall tension

Cardiomyocytes secrete BNP precursor that is cleaved into proBNP

After secretion into ventricles proBNP is cleaved into the active C-terminal portion and the inactive NT-proBNP portion

| | NT-proBNP levels (pg/mL) |
|---|---|
| Age | HF very likely |
| <50 | >450 |
| 50-75 | >900 |
| >75 | >1800 |

Limitations: Age, body habitus, renal function, pulmonary embolism



**Features of Heart Failure on CXR**

**HERB-B**
**H**eart enlargement (cardiothoracic ratio >0.50)
Pleural **E**ffusion
**R**e-distribution (alveolar edema)
Kerley **B** lines
**B**ronchiolar-alveolar cuffing



Patients on β-blocker therapy who have acute decompensated heart failure should continue β-blockers where possible (provided they are not in cardiogenic shock or in severe pulmonary edema)



**Can the Clinical Examination Diagnose Left-Sided Heart Failure in Adults?**
**From The Rational Clinical Examination**
JAMA 2009; http://www.jamaevidence.com/content/3478992
**Study:** Systematic review of articles assessing the accuracy and precision of the clinical exam in the diagnosis of CHF.
**Results:** The diagnosis of left ventricular dysfunction in patient after an MI based on the presence of radiographic pulmonary venous congestion with edema, rales one-third up the lung fields in the absence of a chronic pulmonary disease, or a 3rd heart sound had a positive likelihood ratio (+LR) of 3.1 (95% CI 1.7-5.8) and a negative likelihood ratio (-LR) of 0.62 (95% CI 0.46-0.83). In inpatients the combination of clinical findings, ECG, and CXR had a +LR of 2.0 (95% CI 1.6-2.5) and a –LR of 0.41 (95% CI 0.30-0.56). Female sex (+LR, 1.6 [95% CI 1.2-2.2]) and sBP ≥160 mmHg (+LR, 1.8 [95% CI 1.3-2.6]) were most indicative for diastolic dysfunction. Heart rate ≥100/min (+LR 0.43 [95% CI 0.28-0.65]) and left atrial ECG abnormality (+LR 0.42 [95% CI 0.26-0.63]) were most indicative for systolic dysfunction.
**Conclusions:** Patients with signs, symptoms, and risk factors for systolic dysfunction should receive an ECG and CXR. Female sex and sBP ≥160 mmHg are suggestive of diastolic dysfunction; heart rate ≥100/min and left atrial ECG abnormality suggest systolic dysfunction.

- **Antiarrhythmic drugs**: for use in CHF with arrhythmia
  - can use amiodarone, β-blocker, or digoxin
- **Anticoagulants**: warfarin for prevention of thromboembolic events
  - prior thromboembolic event or AFib, presence of LV thrombus on echo
- **Ivabradine**: selective inhibition of the $I_f$ current
  - recommended for CV death and hospitalization prevention in patients with HFREF and symptomatic despite treatment with appropriate doses of guideline-directed medical therapy (GDMT), with a resting HR >70 bpm, in sinus rhythm and a prior HF hospitalization within 12 mo
- **Hydralazine plus isosorbide dinitrate**: symptom control and mortality benefit in black patients with symptomatic HFREF despite GDMT
  - recommended also for HFREF patients with drug intolerance to ACEI and ARB

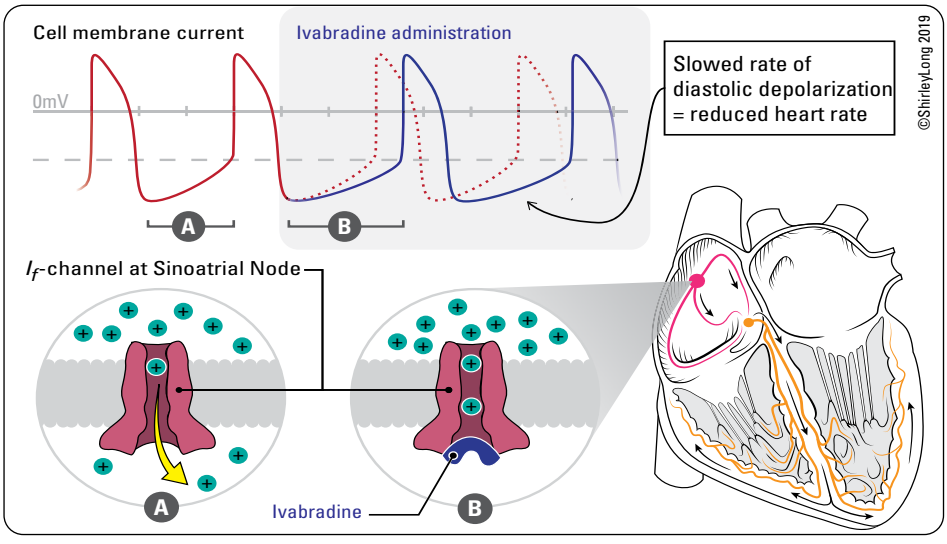



**Figure 40. Ivabradine mechanism of action**

## Procedural Interventions

- resynchronization therapy: symptomatic improvement with biventricular pacemaker
  - consider if QRS >130 msec, LVEF <35%, and persistent symptoms despite optimal therapy
  - greatest benefit likely with marked LV enlargement, mitral regurgitation, QRS >150 msec
- ICD: mortality benefit in 1° prevention of sudden cardiac death
  - prior MI, optimal medical therapy, LVEF <30%, clinically stable
  - prior MI, non-sustained VT, LVEF 30-40%, EPS inducible VT
- LVAD/RVAD (see *Ventricular Assist Devices*, C38)
- cardiac transplantation (see *Cardiac Transplantation*, C38)
- valve repair if patient is surgical candidate and has significant valve disease contributing to CHF (see *Valvular Heart Disease*, C42)

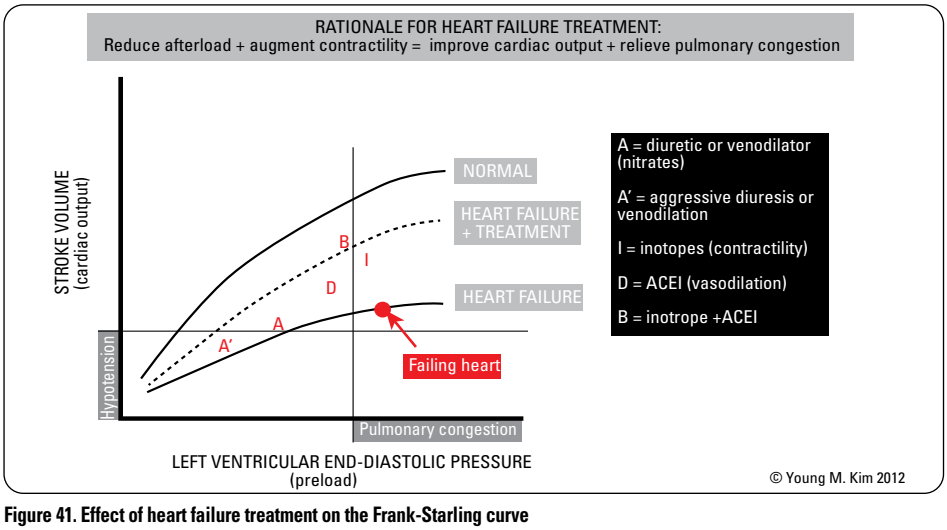



**Figure 41. Effect of heart failure treatment on the Frank-Starling curve**

**Chronic Treatment of CHF**
- ACEI*
- β-blockers*
- ± Mineralocorticoid receptor antagonists*
- Diuretic
- ± Inotrope
- ± Antiarrythmic
- ± Anticoagulant

*Mortality benefit

**Ivabradine and Outcomes in Chronic Heart Failure (SHIFT): A Randomized Placebo-Controlled Study**
Lancet 2010;376:11-17
**Study**: randomised, double-blind, placebo-controlled, parallel-group trial.
**Population**: patients with symptomatic heart failure and LVEF of 35% or lower, in sinus rhythm with HR greater than or equal to 70bpm, had been admitted to hospital for heart failure within previous year, on stable background treatment included beta blocker if tolerated.
**Intervention**: ivabradine titrated to a maximum of 7.5 mg twice daily vs. placebo.
**Outcome**: primary endpoint was composite of cardiovascular death or hospital admission for worsening heart failure.
**Results**: 793 (24%) patients in the ivabradine group and 937 (29%) of those taking placebo had a primary endpoint event (HR 0.82, 95% CI 0.75–0.90, p<0.0001). Fewer serious adverse events occurred in the ivabradine group (3388 events) than in the placebo group (3847; p=0.025). 150 (5%) of ivabradine patients had symptomatic bradycardia vs. 32 (1%) of the placebo group (p<0.0001). Median follow-up was 22.9 (IQR 18–28) months.
**Conclusions**: Results support the importance of heart-rate reduction with ivabradine for improvement of clinical outcomes in heart failure and confirm the important role of heart rate in the pathophysiology of this disorder. Note: Limitation of this study was that only 26% of patients were on target β-blocker doses. Ivabradine currently recommended in these patients when HR is not controlled on maximum tolerated β-blocker dose or there is a contraindication to β-blocker use.

**Higher New York Heart Association Classes and Increased Mortality and Hospitalization in Patients with Heart Failure and Preserved Left Ventricular Function**
Am Heart J 2006;151:444-450
**Purpose**: To establish the association between NYHA class and outcomes with heart failure and preserved systolic function.
**Methods**: Retrospective follow-up study (median 38.5 mo) of 988 patients with heart failure with ejection fracture >45%. Estimated risks of various outcomes using Cox proportional hazard models.
**Results**: Adjusted hazard ratio for all-cause mortality for NYHA class II, III, IV patients was 1.54, 2.56, and 8.46, respectively. Adjusted hazard ratio for all-cause hospitalization for NYHA class II, III, IV patients was 1.23, 1.71, and 3.4, respectively.
**Conclusions**: Higher NYHA classes were associated with poorer outcomes in patients with heart failure and preserved systolic function. Proportions of NYHA I, II, III, and IV patients who died of all causes during the study were 14.3%.

| NYHA | Proportion of All-Cause Hospitalization | Proportion of All-Cause Mortality |
|---|---|---|
| I | 60.7% | 14.3% |
| II | 65.2% | 21.3% |
| III | 77.7% | 35.9% |
| IV | 75.0% | 58.3% |

# Sleep-Disordered Breathing

- patients with CHF can have sleep disturbances; 40% of patients have central sleep apnea with Cheyne-Stokes breathing and 11% of patients have obstructive sleep apnea
- associated with a worse prognosis and greater LV dysfunction
- nasal continuous positive airway pressure (CPAP) is effective in treating symptoms of sleep apnea with secondary beneficial effects in cardiac function and symptoms

# Cardiac Transplantation

- treatment for end-stage heart disease; due to ischemic or non-ischemic cardiomyopathy
- worldwide 1 yr survival is 85-90%, 5 yr survival about 60%, annual mortality rate of 4%
- matching is according to blood type, body size and weight (should be within 25%), and HLA tissue matching (if time allows)

**Effects of Donor Pre-Treatment with Dopamine on Survival After Heart Transplantation: A Cohort Study of Heart Transplant Recipients Nested in a Randomized Controlled Multicentre Trial**
J Am Coll Cardiol 2010;58:1768-1777
Treatment of brain-dead donors with dopamine of 4 μg/kg/min will not harm cardiac allografts but appears to improve the clinical course of the heart allograft recipient.

### Indications for Surgery
- severe cardiac disability despite maximal medical therapy (e.g. recurrent hospitalizations for CHF, NYHA III or IV, peak metabolic oxygen consumption <14 mL/kg/min in absence of β-blocker)
- symptomatic cardiac ischemia refractory to conventional treatment (e.g. unstable angina not amenable to CABG or PCI with LVEF <30%; recurrent, symptomatic ventricular arrhythmias)
- cardiogenic shock requiring IV inotropic agents or mechanical circulatory support to sustain organ perfusion
- exclusion of all surgical alternatives to cardiac transplantation

### Contraindications (*indicates absolute contraindications)
- incurable malignancy*
- major systemic illness*
- irreversible major organ disease*
- active systemic infection
- obesity
- irreversible pulmonary HTN (pulmonary vascular resistance [PVR] >6 Wood units)*
- severe COPD (FEV1 <1 L)*
- active drug addiction or alcoholism*

### Prerequisites
- psychosocial stability
- medically compliant and motivated

**REMATCH Trial**
NEJM 2001;345:1435-1443
Increased survival of 23% vs. 8% with LVAD vs. medical management of heart failure after 2 yr. Heartmate VAD has a biologic surface, therefore, does not require long-term anticoagulation but higher risk of infection

### Complications
- rejection
  - common, <5% have serious hemodynamic compromise
  - gold standard to detect rejection: endomyocardial biopsy
  - risk of acute rejection is greatest during the first 3 mo after transplant
- infection
  - leading cause of morbidity and mortality after cardiac transplantation
  - risk peaks early during the first few months after transplantation and then declines to a low persistent rate
- allograft vasculopathy
  - approximately 50% develop graft vasculopathy within 10 yr of transplantation
  - most common cause of late death following transplantation
- malignancy
  - develops in 15% of cardiac transplant recipients due to immunosuppressive medication
  - second most common cause of late death following transplantation
  - cutaneous neoplasms most common, followed by non-Hodgkin's lymphoma and lung cancer
- immunosuppressive medication side effects (prednisone, cyclosporine, tacrolimus, sirolimus)

**Canadian Cardiovascular Society Focused Position Statement Update on Assessment of the Cardiac Patient for Fitness to Drive: Fitness following Left Ventricular Assist Device Implantation**
Can J Cardiol 2012;28:137-140
Patients with a continuous flow, NYHA class I-III, LVAD that are stable 2 mo post LVAD implantation qualify for private driving only and are disqualified from commercial driving.

# Ventricular Assist Devices

- work to unload the ventricle while maintaining output; also results in decreased myocardial oxygen consumption permitting recovery of the myocardium that is not irreversibly injured
- can support the left (LVAD), right (RVAD), or both ventricles (BiVAD)
- indications:
  - bridge to transplantation, bridge to decision (for transplant), or long term permanent therapy ("destination therapy")
  - post-operative mechanical support when unable to separate from cardiopulmonary bypass despite inotropic and intra-aortic balloon pump (IABP) support
    - IABP is a catheter based device inserted into the femoral artery and advanced to the descending aorta that decreases myocardial $O_2$ demand and increases blood flow to coronary arteries
    - inflation of the balloon occurs during diastole to increase ascending aorta and coronary artery perfusion pressure; deflation occurs at systole to reduce intra-aortic pressure thus reducing afterload
    - cardiogenic shock

# Myocardial Disease

## Definition of Cardiomyopathy

- intrinsic or primary myocardial disease not secondary to congenital, hypertensive, coronary, valvular, or pericardial disease
- functional classification: dilated, hypertrophic, or restrictive
- LV dysfunction 2º to MI, often termed "ischemic cardiomyopathy", is not a true cardiomyopathy (i.e. primary myocardial disorder) since the primary pathology is obstructive CAD

**Table 14. Summary Table for CHF and Myocardial Disease**

| Heart Failure Reduced Ejection Fraction | | Heart Failure Preserved Ejection Fraction | | |
|---|---|---|---|---|
| **Dilated Cardiomyopathy** | **Secondary Causes** | **Hypertrophic Cardiomyopathy** | **Restrictive Cardiomyopathy** | **Secondary Causes** |
| Idiopathic, infectious (e.g. myocarditis), alcohol, familial, collagen vascular disease | CAD, MI, DM, valvular (e.g. AR, MR) | Genetic disorder affecting cardiac sarcomeres (most common cause of sudden cardiac death in young athletes) | Amyloidosis, sarcoidosis, scleroderma, hemochromatosis, Fabry's, Pompe's Disease, Loeffler's | HTN, DM, valvular (e.g. AS), post-MI, transiently by ischemia |



**Cardiomyopathy**

**HARD**
**H**ypertrophic cardiomyopathy
**A**rrhythmogenic right ventricular cardiomyopathy
**R**estrictive cardiomyopathy
**D**ilated cardiomyopathy

# Myocarditis

## Definition

- inflammatory process involving the myocardium ranging from acute to chronic; an important cause of dilated cardiomyopathy

## Etiology

- idiopathic
- infectious
  - viral (most common): parvovirus B19, influenza, coxsackie B, echovirus, poliovirus, HIV, mumps
  - bacterial: *S. aureus, C. perfringens, C. diphtheriae, Mycoplasma, Rickettsia*
  - fungi
  - spirochetal (Lyme disease – *Borrelia burgdorferi*)
  - Chagas disease (*Trypanosoma cruzi*), toxoplasmosis
- toxic: catecholamines, chemotherapy, cocaine
- hypersensitivity/eosinophilic: drugs (e.g. antibiotics, diuretics, lithium, clozapine), insect/snake bites
- systemic diseases: collagen vascular diseases (e.g. SLE, rheumatoid arthritis), sarcoidosis, autoimmune
- other: giant cell myocarditis, acute rheumatic fever

## Signs and Symptoms

- constitutional symptoms
- acute CHF: dyspnea, tachycardia, elevated JVP
- chest pain: due to pericarditis or cardiac ischemia
- arrhythmias
- systemic or pulmonary emboli
- pre-syncope/syncope/sudden death

## Investigations

- ECG: non-specific ST-T changes ± conduction defects
- blood work
  - increased CK, troponin, LDH, and AST with acute myocardial necrosis ± increased WBC, ESR, ANA, rheumatoid factor, complement levels
  - blood culture, viral titres, and cold agglutinins for *Mycoplasma*
- CXR: enlarged cardiac silhouette
- echo: dilated, hypokinetic chambers, segmental wall motion abnormalities
- cardiovascular magnetic resonance: functional and morphological abnormalities as well as tissue pathology (gadolinium enhancement)
- myocardial biopsy

## Management

- supportive care
- restrict physical activity
- treat CHF
- treat arrhythmias
- anticoagulation
- treat underlying cause if possible

## Prognosis

- often unrecognized and may be self-limited
- myocarditis treatment trial showed 5 yr mortality between 25-50%
- giant cell myocarditis, although rare can present with fulminant CHF and be rapidly fatal, with 5 yr mortality >80%
- sudden death in young adults
- may progress to dilated cardiomyopathy

# Dilated Cardiomyopathy

### Definition
- unexplained dilation and impaired systolic function of one or both ventricles

### Etiology
- idiopathic (presumed viral or idiopathic) ~50% of DCM
- alcohol
- familial/genetic
- uncontrolled tachycardia (e.g. persistent rapid AFib)
- collagen vascular disease: SLE, polyarteritis nodosa, dermatomyositis, progressive systemic sclerosis
- infectious: viral (coxsackie B, HIV), Chagas disease, Lyme disease, Rickettsial diseases, acute rheumatic fever, toxoplasmosis
- neuromuscular disease: Duchenne muscular dystrophy, myotonic dystrophy, Friedreich's ataxia
- metabolic: uremia, nutritional deficiency (thiamine, selenium, carnitine)
- endocrine: hyper/hypothyroidism, DM, pheochromocytoma
- peripartum
- toxic: cocaine, heroin, organic solvents
- drugs: chemotherapies (doxorubicin, cyclophosphamide), anti-retrovirals, chloroquine, clozapine, TCA
- radiation

**Major Risks Factors for DCM**
Alcohol, cocaine, family history

**Abnormal Labs in DCM**
- High BNP
- High Cr
- High LFTs
- Low bicarbonate
- Low $Na^+$

### Signs and Symptoms
- may present as:
  - CHF
  - systemic or pulmonary emboli
  - arrhythmias
  - sudden death (major cause of mortality due to fatal arrhythmia)

### Investigations
- blood work: CBC, electrolytes, Cr, bicarbonate, BNP, CK, troponin, LFTs, TSH, TIBC
- ECG: variable ST-T wave abnormalities, poor R wave progression, conduction defects (e.g. BBB), arrhythmias (e.g. non-sustained VT)
- CXR: global cardiomegaly (i.e. globular heart), signs of CHF, pleural effusion
- echo: chamber enlargement, global hypokinesis, depressed LVEF, MR and TR, mural thrombi
- endomyocardial biopsy: not routine, used to rule out a treatable cause
- coronary angiography: in selected patients to exclude ischemic heart disease

### Management
- treat underlying disease: e.g. abstinence from alcohol
- treat CHF: see *Heart Failure*, C34
- thromboembolism prophylaxis: anticoagulation with warfarin
  - indicated for: AFib, history of thromboembolism or documented thrombus
- treat symptomatic or serious arrhythmias
- immunize against influenza and *S. pneumoniae*
- consider surgical options (e.g. LVAD, transplant, volume reduction surgery) in appropriate candidates with severe, drug refractory disease
- consider ICD among patients with a LVEF <30%

### Prognosis
- depends on etiology
- better with reversible underlying cause, worst with infiltrative diseases, HIV, drug-induced
- cause of death usually CHF (due to pump failure) or sudden death 2° to ventricular arrhythmias
- systemic emboli are significant source of morbidity
- 20% mortality in 1st yr, 10% per year thereafter

# Hypertrophic Cardiomyopathy

- see *2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy* for details

### Definition
- defined as unexplained ventricular hypertrophy
- various patterns of HCM are classified, but most causes involve pattern of septal hypertrophy

### Etiology and Pathophysiology
- histopathologic features include myocyte disarray, myocyte hypertrophy, and interstitial fibrosis
- cause is felt to be a genetic defect involving one of the cardiac sarcomeric proteins (>400 mutations associated with autosomal dominant inheritance, incomplete penetrance)
- prevalence of 1/500-1/1000 in general population
- generally presents in early adulthood

### Hemodynamic Classification
- hypertrophic obstructive cardiomyopathy (HOCM): dynamic LV outflow tract (LVOT) obstruction, either at rest or with provocation, defined as LVOT gradient of at least 30 mmHg
  - dynamic i.e. obstruction (and the murmur) is reduced with maneuvers that increase preload and augmented with maneuvers that reduce preload

- non-obstructive HCM: no LVOT obstruction
- many patients have diastolic dysfunction (impaired ventricular filling secondary to LV hypertrophy which decreases compliance)

### Signs and Symptoms
- clinical manifestations: asymptomatic (common, therefore screening is important), shortness of breath on exertion (SOBOE), angina, presyncope/syncope (due to LV outflow obstruction or arrhythmia), CHF, arrhythmias, SCD
- pulses: rapid upstroke, "spike and dome" pattern in carotid pulse (in HCM with outflow tract obstruction)
- precordial palpation: PMI localized, sustained, double impulse, 'triple ripple' (triple apical impulse in HOCM), LV lift
- precordial auscultation: normal or paradoxically split S2, S4, harsh systolic diamond-shaped murmur at LLSB or apex, enhanced by squat to standing or Valsalva (murmur secondary to LVOT obstruction as compared to AS); often with pansystolic murmur due to mitral regurgitation

### Investigations
- ECG/Holter monitor: LVH, high voltages across precordium, prominent Q waves (lead I, aVL, V5, V6), tall R wave in V1, P wave abnormalities
- transthoracic echocardiography and echo-Doppler study: asymmetric septal hypertrophy (less commonly apical), systolic anterior motion (SAM) of mitral valve and MR; LVOT gradient can be estimated by Doppler measurement
- genetic studies (± magnetic resonance imaging) can be helpful when echocardiography is inconclusive for diagnosis
- cardiac catheterization (only when patient being considered for invasive therapy)

### Management
- avoid factors which increase obstruction (e.g. volume depletion)
  - avoidance of all competitive sports
- treatment of obstructive HCM
  - medical agents: β-blockers, disopyramide, verapamil (started only in monitored setting), phenylephrine (in setting of cardiogenic shock)
  - avoid nitrates, diuretics, and ACEI as they increase LVOT gradient and worsen symptoms
- patients with obstructive HCM and drug-refractory symptoms
  - surgical myectomy
  - alcohol septal ablation - percutaneous intervention that ablates the hypertrophic septum with 100% ethanol via the septal artery
  - dual chamber pacing (rarely done)
- treatment of patients at high risk of sudden death: ICD
- first-degree relatives (children, siblings, parents) of patients with HCM should be screened (physical, ECG, 2D echo) every 12-18 mo during adolescence, then serially every 5 yr during adulthood

### Prognosis
- potential complications: AFib, VT, CHF, sudden cardiac death (1% risk/yr; most common cause of SCD in young athletes)
  - major risk factors for sudden death (consider ICD placement)
  - history of survived cardiac arrest/sustained VT
  - family history of multiple premature sudden deaths
  - other factors associated with increased risk of sudden cardiac death
    - syncope (presumed to be arrhythmic in origin)
    - non-sustained VT on ambulatory monitoring
    - marked ventricular hypertrophy (maximum wall thickness ≥30 mm)
    - abnormal BP in response to exercise (in patients <40 yr old with HCM)



**RCM vs. Constrictive Pericarditis (CP)**
Present similarly but CP is treatable with surgery

## Restrictive Cardiomyopathy

### Definition
- impaired ventricular filling with preserved systolic function in a non-dilated, non-hypertrophied ventricle secondary to factors that decrease myocardial compliance (fibrosis and/or infiltration)



**Key Investigations**
- Echo: may show respiratory variation in blood flow in CP
- CT: may show very thickened pericardium and calcification in CP
- MRI: best modality to directly visualize pericardium and myocardium

### Etiology
- infiltrative: amyloidosis, sarcoidosis
- non-infiltrative: scleroderma, idiopathic myocardial fibrosis
- storage diseases: hemochromatosis, Fabry's disease, Gaucher's disease, glycogen storage diseases
- endomyocardial
  - endomyocardial fibrosis, Loeffler's endocarditis, or eosinophilic endomyocardial disease
  - radiation heart disease
  - carcinoid syndrome (may have associated tricuspid valve or pulmonary valve dysfunction)

### Clinical Manifestations
- CHF (usually with preserved LV systolic function), arrhythmias
- elevated JVP with prominent x and y descents, Kussmaul's sign
- S3, S4, MR, TR
- thromboembolic events

### Investigations
- ECG: low voltage, non-specific, diffuse ST-T wave changes ± non-ischemic Q waves
- CXR: mild cardiac enlargement
- Echo: LAE, RAE; specific Doppler findings with no significant respiratory variation
- cardiac catheterization: increased end-diastolic ventricular pressures
- endomyocardial biopsy: to determine etiology (especially for infiltrative RCM)

### Management
- exclude constrictive pericarditis
- treat underlying disease: control HR, anticoagulate if AFib
- supportive care and treatment for CHF, arrhythmias
- cardiac transplant: might be considered for CHF refractory to medical therapy

### Prognosis
- depends on etiology

# Valvular Heart Disease

- see the *2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease*. JACC Jul 11;70(2):252-289 for details

### Infective Endocarditis
- see Infectious Diseases, ID13
- American Heart Association (AHA) 2007 guidelines recommend IE prophylaxis
  - only for patients with:
    - prosthetic valve material
    - past history of IE
    - certain types of congenital heart disease
    - cardiac transplant recipients who develop valvulopathy
  - only for the following procedures:
    - dental
    - respiratory tract
    - procedures on infected skin/skin structures/MSK structures
    - not GI/GU procedures specifically

# Rheumatic Fever

- see Pediatrics, P56

### Prognosis
- acute complications: myocarditis (DCM/CHF), conduction abnormalities (sinus tachycardia, AFib), valvulitis (acute MR), acute pericarditis (not constrictive pericarditis)
- chronic complications: rheumatic valvular heart disease – fibrous thickening, adhesion, calcification of valve leaflets resulting in stenosis/regurgitation, increased risk of IE ± thromboembolism
- onset of symptoms usually after 10-20 yr latency from acute carditis of rheumatic fever
- mitral valve most commonly affected

# Valve Repair and Valve Replacement

- indication for valve repair or replacement depends on the severity of the pathology; typically recommended when medical management has failed to adequately improve the symptoms or reduce the risk of morbidity and mortality
- pathologies that may require surgical intervention include congenital defects, infections, rheumatic heart disease as well as a variety of valve diseases associated with aging (i.e. degenerative valve lesions)
- valve repair: surgical valvuloplasty (commissurotomy, annuloplasty), chordae tendineae repair, tissue patch
- valve replacement: typically for aortic or mitral valves only; mitral valve repair is favoured in younger individuals (and patients with mitral valve prolapse with severe mitral regurgitation)
- percutaneous techniques are being established to replace or repair valves
- decision between mechanical vs. bioprosthetic prosthesis for patients 50-70 yr old remains uncertain as valve techniques evolve

# Choice of Valve Prosthesis

**Table 15. Mechanical Valve vs. Bioprosthetic Valve**

| Mechanical Valve | Bioprosthetic Valve |
|---|---|
| Good durability | Limited long-term durability (mitral<aortic) |
| Less preferred in small aortic root sizes | Good flow in small aortic root sizes |
| Increased risk of thromboembolism (1-3%/yr): requires long-term anticoagulation with coumadin | Decreased risk of thromboembolism: long-term anticoagulation not needed for aortic valves |
| Target INR Aortic valves: 2.0-3.0 (mean 2.5)<br>Mitral valves: 2.5-3.5 (mean 3.0) | Some recommendation for limited anticoagulation for mitral valves |
| Increased risk of hemorrhage: 1-2%/yr | Decreased risk of hemorrhage |
| ≤50 yr | Any age |



**Mitral Valve Repair vs. Replacement for Severe Ischemic Mitral Regurgitation**
NEJM 2014;370:23-32
**Purpose**: Ischemic mitral regurgitation is associated with significant mortality risk. The purpose of this study was to compare the effectiveness and safety of repairing versus replacing the mitral valve in patients with severe chronic ischemic mitral regurgitation.
**Study Design**: RCT with 251 patients with severe ischemic mitral regurgitation were randomly assigned to mitral valve repair or chordal-sparing replacement. The primary endpoint was the left ventricular end-systolic volume index (LVESVI) at 12 mo.
**Results**: There were no significant between-group differences in LVESVI, in the rate of major adverse cardiac or cerebrovascular events, in functional status, or in quality of life at 12 mo. The rate of moderate or severe mitral regurgitation recurrence at 12 mo was significantly higher in the repair group than in the replacement group (32.6% vs. 2.3%, respectively).
**Conclusions**: No significant difference in left ventricular reverse modelling or survival at 12 mo between patients who underwent mitral valve repair or replacement. Replacement provided more durable correction of mitral regurgitation, but there were no significant differences in clinical outcomes.

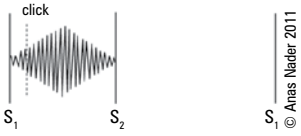
# Prosthetic Valve Management

- follow-up
  - TTE after prosthetic valve implantation to assess hemodynamics
  - anticoagulation and INR monitoring for patients with a mechanical valve
  - no known medical therapies to prevent bioprosthetic valve degeneration
  - TEE or repeat TTE when clinical symptoms or signs suggest prosthetic valve dysfunction
  - annual TTE is reasonable in asymptomatic patients with a bioprosthetic valve after the first 10 yr
- bioprosthetic valve dysfunction
  - etiology: tissue degeneration, pannus formation, IE, thrombosis
  - presentation: exertional dyspnea, louder systolic murmur, new diastolic murmur
  - investigations: TTE
  - treatment: depends on the type and severity of the pathology as well as patient characteristics
    - surgical intervention (thrombosed left-sided valve, severe valve stenosis, or regurgitation)
    - fibrinolytic therapy (thrombosed valve)
    - transcatheter valve-in-valve procedure (severely symptomatic aortic stenosis at high or prohibitive risk of reoperation)
- mechanical valve dysfunction
  - etiology: thrombosis, pannus formation, IE, suture disruption
  - presentation: symptoms of HF, systemic thromboembolism, hemolysis, new murmur
  - investigations: urgent multimodal imaging for suspected valve thrombosis (TTE, TEE, fluoroscopy, and/or CT), otherwise TTE
  - treatment: depends on the type and severity of the pathology as well as patient characteristics
    - surgical intervention (thrombosed left-sided valve, severe valve stenosis, or regurgitation)
    - fibrinolytic therapy (thrombosed valve)

# Summary of Valvular Disease

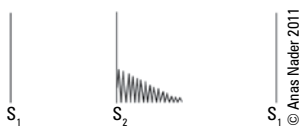
**Table 16. Valvular Heart Disease**

## Aortic Stenosis (AS)




**Etiology**
Congenital (bicuspid, unicuspid valve), calcification (wear and tear), rheumatic disease
**Definition**
Normal aortic valve area = 3-4 $cm^2$
Mild AS >1.5 $cm^2$
Moderate AS 1.0 to 1.5 $cm^2$
Severe AS <1.0 $cm^2$
Critical AS <0.5 $cm^2$
**Pathophysiology**
Outflow obstruction → increased EDP → concentric LVH → LV failure → CHF, subendocardial ischemia
**Symptoms**
Exertional angina, syncope, dyspnea, PND, orthopnea, peripheral edema
**Physical Exam**
Narrow pulse pressure, brachial-radial delay, pulsus parvus et tardus, sustained PMI
Auscultation: crescendo-decrescendo SEM radiating to R clavicle and carotid, musical quality at apex (Gallavardin phenomenon), S4, soft S2 with paradoxical splitting, S3 (late)
**Investigations**
ECG: LVH and strain, LBBB, LAE, AFib
CXR: post-stenotic aortic root dilatation, calcified valve, LVH, LAE, CHF
Echo: reduced valve area, pressure gradient, LVH, reduced LV function
**Treatment**
Asymptomatic: serial echos, avoid exertion
Symptomatic: avoid nitrates/arterial dilators and ACEI in severe AS
Surgery if: symptomatic or asymptomatic severe AS with low-to-intermediate surgical risk and who meet an indication (survival benefit, symptom improvement, and improvement in LV systolic function)
**Surgical Options**
Valve replacement: aortic rheumatic valve disease and trileaflet valve
– prior to pregnancy (if AS significant)
– balloon valvuloplasty (in very young or as a bridge to valve replacement for symptomatic patients with severe AS)
**Interventional Options**
Percutaneous valve replacement (transfemoral or transapical approach) is an option in selected symptomatic patients with severe AS who are at an intermediate to prohibitive risk for surgery with a predicted post-procedure survival ≥12 mo

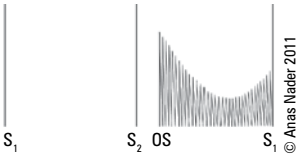
## Aortic Regurgitation (AR)




**Etiology**
Supravalvular: aortic root disease (Marfan's, atherosclerosis and dissectin( aneurysm, connective tissue disease)
Valvular: congenital (bicuspid aortic valv large VSD), IE
Acute Onset: IE, aortic dissection, trauma, failed prosthetic valve
**Pathophysiology**
Volume overload → LV dilatation → increased SV, high sBP and low dBP → increased wall tension → pressure overload → LVH (low dBP → decreased coronary perfusion)
**Symptoms**
Usually only becomes symptomatic late in disease when LV failure develops
Dyspnea, orthopnea, PND, syncope, angina
**Physical Exam**
Waterhammer pulse, bisferiens pulse, femoral-brachial sBP >20 mmHg (Hill's test wide pulse pressure), hyperdynamic apex, displaced PMI, heaving apex
Auscultation: early decrescendo diastolic murmur at LLSB (cusp pathology) or RLSB (aortic root pathology), best heard sitting, leaning forward, on full expiration, soft S1, absent S2, S3 (late)
**Investigations**
ECG: LVH, LAE
CXR: LVH, LAE, aortic root dilatation
Echo/TTE: quantify AR, leaflet or aortic root anomalies
Cath: if >40 yr and surgical candidate – to assess for ischemic heart disease
Exercise testing: hypotension with exercise
**Treatment**
Asymptomatic: serial echos, afterload reduction (e.g. ACEI, nifedipine, hydralazine)
Symptomatic: avoid exertion, treat CHF
Surgery if: NYHA class III-IV CHF; LV dilatation and/or LVEF <50% with/without symptoms
**Surgical Options**
Valve replacement: most patients
Valve repair: very limited role
Aortic root replacement (Bentall procedure):
– when ascending aortic aneurysm present, valved conduit used

**Table 16. Valvular Heart Disease** (continued)

## Mitral Stenosis (MS)



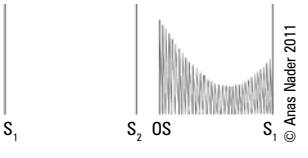

**Etiology**
Rheumatic disease most common cause, congenital (rare)
**Definition**
Severe MS is mitral valve area (MVA) <1.5 $cm^2$
**Pathophysiology**
MS → fixed CO and LAE → increased LA pressure → pulmonary vascular resistance and CHF; worse with AFib (no atrial kick), tachycardia (decreased atrial emptying time) and pregnancy (increased preload)
**Symptoms**
SOB on exertion, orthopnea, fatigue, palpitations, peripheral edema, malar flush, pinched and blue facies (severe MS)
**Physical Exam**
AFib, no "a" wave on JVP, left parasternal lift, palpable diastolic thrill at apex
Auscultation: mid-diastolic rumble at apex, best heard with bell in left lateral decubitus position following exertion, loud S1, OS following loud P2 (heard best during expiration), long diastolic murmur, and short A2-OS interval correlate with worse MS
**Investigations**
ECG: NSR/AFib, LAE (P mitrale), RVH, RAD
CXR: LAE, CHF, mitral valve calcification
Echo/TTE: shows restricted opening of mitral valve
Cath: indicated in concurrent CAD if >40 yr (male) or >50 yr (female)
**Treatment**
Avoid exertion, fever (increased LA pressure), treat AFib and CHF, increase diastolic filling time (β-blockers, digitalis)
Surgery if: NYHA class III-IV CHF and failure of medical therapy
**Invasive Options**
Percutaneous balloon valvuloplasty: young rheumatic pts and good leaflet morphology (can be determined by echo), asymptomatic pts with moderate-severe MS, pulmonary HTN
Contraindication: left atrial thrombus, moderate MR
Open Mitral Commissurotomy: if mild calcification + leaflet/chordal thickening – restenosis in 50% pts in 8 yr
Valve replacement: indicated in moderate-severe calcification and severely scarred leaflets

## Mitral Regurgitation (MR)




**Etiology**
Mitral valve prolapse, congenital cleft leaflets, LV dilatation/aneurysm (CHF, DCM, myocarditis), IE abscess, Marfan's syndrome, HOCM, acute MI, myxoma, mitral valve annulus calcification, chordae/papillary muscle trauma/ischemia/rupture (acute), rheumatic disease
**Pathophysiology**
Reduced CO → increased LV and LA pressure → LV and LA dilatation → CHF and pulmonary HTN
**Symptoms**
Dyspnea, PND, orthopnea, palpitations, peripheral edema
**Physical Exam**
Displaced hyperdynamic apex, left parasternal lift, apical thrill
Auscultation: holosystolic murmur at apex, radiating to axilla ± mid-diastolic rumble, loud S2 (if pulmonary HTN), S3
**Investigations**
ECG: LAE, left atrial delay (bifid P waves), ± LVH
CXR: LVH, LAE, pulmonary venous HTN
Echo: etiology and severity of MR, LV function, leaflets
Swan-Ganz Catheter: prominent LA "v" wave
**Treatment**
Asymptomatic: serial echos
Symptomatic: decrease preload (diuretics), decrease afterload (ACEI) for severe MR and poor surgical candidates; stabilize acute MR with vasodilators before surgery
Surgery if: acute MR with CHF, papillary muscle rupture, NYHA class III-IV CHF, AF, increasing LV size or worsening LV function, earlier surgery if valve repairable (>90% likelihood) and patient is low-risk for surgery
**Surgical Options**
Valve repair: >75% of pts with MR and myxomatous mitral valve prolapse – annuloplasty rings, leaflet repair, chordae transfers/shorten/replacement
Valve replacement: failure of repair, heavily calcified annulus
Advantage of repair: low rate of endocarditis, no anticoagulation, less chance of re-operation

## Tricuspid Stenosis (TS)




**Etiology**
Rheumatic disease, congenital, carcinoid syndrome, fibroelastosis; usually accompanied by MS (in RHD)
**Pathophysiology**
Increased RA pressure → right heart failure → decreased CO and fixed on exertion
**Symptoms**
Peripheral edema, fatigue, palpitations
**Physical Exam**
Prominent "a" waves in JVP, +ve abdominojugular reflux, Kussmaul's sign, diastolic rumble 4th left intercostal space
**Investigations**
ECG: RAE
CXR: dilatation of RA without pulmonary artery enlargement
Echo: diagnostic
**Treatment**
Preload reduction (diuretics), slow HR
Surgery if: only if other surgery required (e.g. mitral valve replacement)
**Surgical Options**
Valve Replacement:
– if severely diseased valve
– bioprosthesis preferred

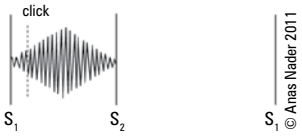
## Tricuspid Regurgitation (TR)




**Etiology**
RV dilatation, IE (particularly due to IV drug use), rheumatic disease, congenital (Ebstein anomaly), carcinoid
**Pathophysiology**
RV dilatation → TR further RV dilatation → right heart failure
**Symptoms**
Peripheral edema, fatigue, palpitations
**Physical Exam**
"cv" waves in JVP, +ve abdominojugular reflux, holosystolic murmur at LLSB accentuated by inspiration, left parasternal lift
**Investigations**
ECG: RAE, RVH, AFib
CXR: RAE, RV enlargement
Echo: diagnostic
**Treatment**
Preload reduction (diuretics)
Surgery if: only if other surgery required (e.g. mitral valve replacement)
**Surgical Options**
Annuloplasty (i.e. repair, rarely replacement)

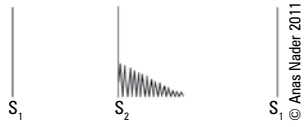
**Table 16. Valvular Heart Disease** (continued)

## Pulmonary Stenosis (PS)



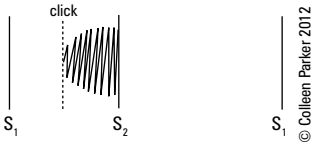

**Etiology**
Usually congenital, rheumatic disease (rare), carcinoid syndrome
**Pathophysiology**
Increased RV pressure → RV hypertrophy → right heart failure
**Symptoms**
Chest pain, syncope, fatigue, peripheral edema
**Physical Exam**
Systolic murmur at 2nd left intercostal space accentuated by inspiration, pulmonary ejection click, right-sided S4
**Investigations**
ECG: RVH
CXR: prominent pulmonary arteries enlarged RV
Echo: diagnostic
**Treatment**
Balloon valvuloplasty if severe symptoms
**Surgical Options**
Percutaneous or open balloon valvuloplasty

## Pulmonary Regurgitation (PR)




**Etiology**
Pulmonary HTN, IE, rheumatic disease, tetrology of Fallot (post-repair)
**Pathophysiology**
Increased RV volume → increased wall tension → RV hypertrophy → right heart failure
**Symptoms**
Chest pain, syncope, fatigue, peripheral edema
**Physical Exam**
Early diastolic murmur at LLSB, Graham Steell (diastolic) murmur 2nd and 3rd left intercostal space increasing with inspiration
**Investigations**
ECG: RVH
CXR: prominent pulmonary arteries if pulmonary HTN; enlarged RV
Echo: diagnostic
**Treatment**
Rarely requires treatment; valve replacement (rarely done)
**Surgical Options**
Pulmonary valve replacement

## Mitral Valve Prolapse (MVP)




**Etiology**
Myxomatous degeneration of chordae, thick, bulky leaflets that crowd orifice, associated with Marfan's syndrome, pectus excavatum, straight back syndrome, other MSK abnormalities; <3% of population
**Pathophysiology**
Mitral valve displaced into LA during systole; no causal mechanisms found for symptoms
**Symptoms**
Prolonged, stabbing chest pain, dyspnea, anxiety/panic, palpitations, fatigue, presyncope
**Physical Exam**
Auscultation: mid-systolic click (due to billowing of mitral leaflet into LA; tensing of redundant valve tissue); mid to late systolic murmur at apex, accentuated by Valsalva or squat-to-stand maneuvers
**Investigations**
ECG: non-specific ST-T wave changes, paroxysmal SVT, ventricular ectopy
Echo: systolic displacement of thickened mitral valve leaflets into LA
**Treatment**
Asymptomatic: no treatment; reassurance
Symptomatic: β-blockers and avoidance of stimulants (caffeine) for significant palpitations, anticoagulation if AFib
**Surgical Options**
Mitral valve surgery (repair favoured over replacement) if symptomatic and significant MR

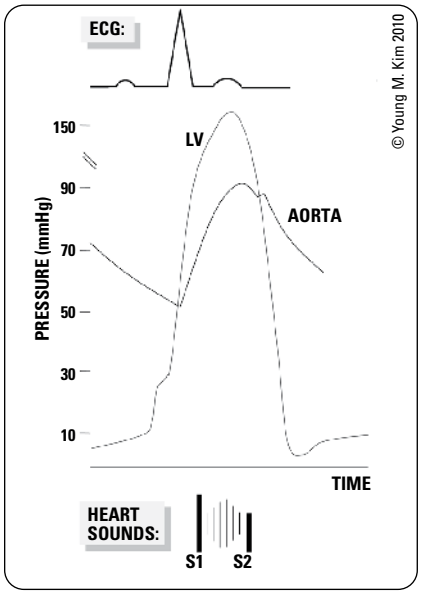



**Figure 42. Hemodynamics of aortic stenosis**
Stenosis across the aortic valve results in the generation of a significant pressure gradient between the left ventricle and the aorta and a crescendo-decrescendo murmur during systolic contraction. The stenosis decreases the intensity of aortic valve closure hence diminishing S2

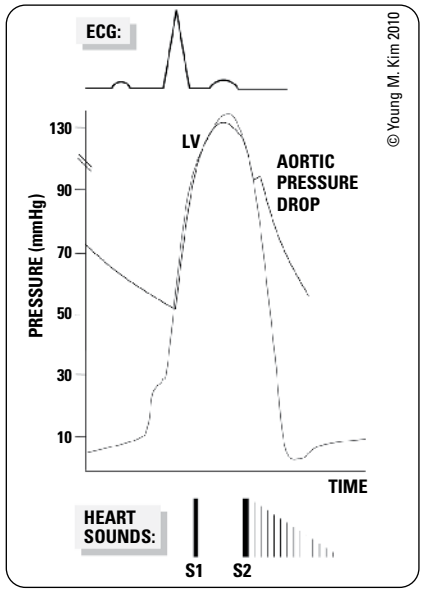



**Figure 43. Hemodynamics of aortic regurgitation**
Regurgitation across the aortic valve during diastole causes the aortic pressure to rapidly decrease and a decrescendo murmur can be heard at the onset of diastole (after S2 is audible). The presence of regurgitant blood from the aorta increases left-ventricular end-diastolic volume

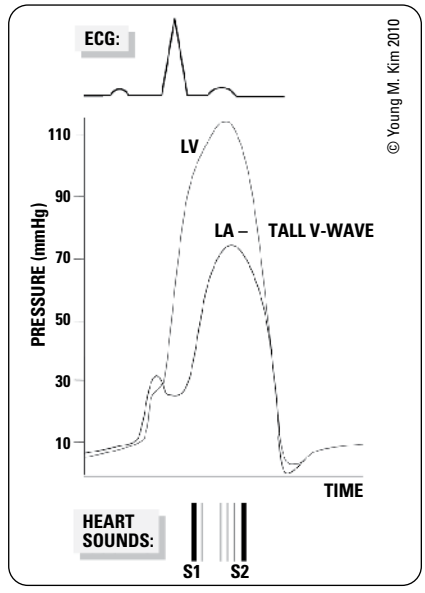



**Figure 44. Hemodynamics of acute mitral regurgitation**
During systolic contraction, blood regurgitates from the left ventricle into the left atrium across the incompetent mitral valve resulting in an audible holosystolic murmur between S1 and S2. The portion of left ventricular end diastolic volume that regurgitates into the left atrial myocardium increases left atrial pressures resulting in a tall V-wave (in the JVP)

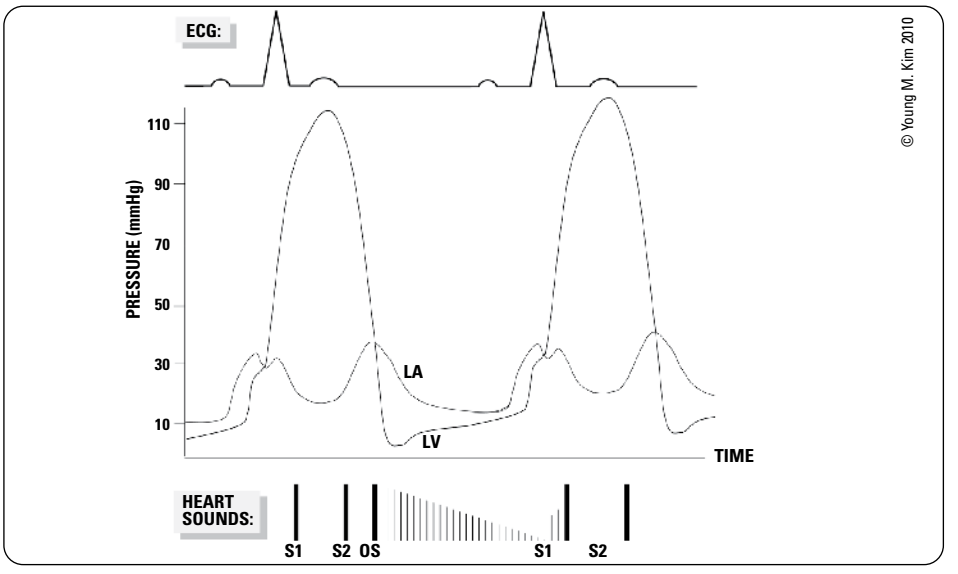



**Figure 45. Hemodynamics of mitral stenosis**
First note that the left atrial pressure exceeds the left ventricular pressure during diastole due to mitral stenosis and the consequent generation of a pressure gradient across the left atrium and left ventricle. In diastole, the stenotic mitral valve opens which corresponds to the opening snap (OS) and the passage of blood across the mitral stenosis results in an audible decrescendo murmur. Left atrial contraction prior to S1 increases the pressure gradient resulting in accentuation of the murmur before S1 is audible

# Pericardial Disease

## Acute Pericarditis

### Etiology of Pericarditis/Pericardial Effusion
- idiopathic is most common: presumed to be viral
- infectious
  - viral: Coxsackie virus A, B (most common), echovirus
  - bacterial: *S. pneumoniae, S. aureus*
  - TB
  - HIV
- fungal: histoplasmosis, blastomycosis
- post-MI: acute (direct extension of myocardial inflammation, 1-7 d post-MI), Dressler's syndrome (autoimmune reaction, 2-8 wk post-MI)
- post-cardiac surgery (e.g. CABG), other trauma
- metabolic: uremia (common), hypothyroidism
- neoplasm: Hodgkin's, breast, lung, renal cell carcinoma, melanoma
- collagen vascular disease: SLE, polyarteritis, rheumatoid arthritis, scleroderma
- vascular: dissecting aneurysm
- other: drugs (e.g. hydralazine), radiation, infiltrative disease (e.g.sarcoid), vaccination (e.g. smallpox)

### Signs and Symptoms
- diagnostic triad: chest pain, friction rub, and ECG changes (i.e. diffuse ST elevation and PR depression with reciprocal changes in aVR)
- pleuritic chest pain: alleviated by sitting up and leaning forward
- pericardial friction rub: may be uni-, bi-, or triphasic; evanescent and rare
- ± fever, malaise

### Investigations
- ECG: initially diffuse elevated ST segments ± depressed PR segment, the elevation in the ST segment is concave upwards → 2-5 d later ST isoelectric with T wave flattening and inversion
- CXR: normal heart size, pulmonary infiltrates
- Echo: performed to assess for pericardial effusion
- biomarkers: troponin I elevation may suggest myopericarditis

**Acute Pericarditis Triad**
- Chest pain
- Friction rub
- ECG changes

### Treatment
- treat the underlying disease
- anti-inflammatory agents (i.e. high dose NSAIDs/ASA; steroid use controversial), analgesics
- colchicine reduces the rate of incessant/recurrent pericarditis (ICAP N Engl J Med 2013; 369:1522-1528)
- physical activity restriction until symptom resolution

### Complications
- recurrent episodes of pericarditis, atrial arrhythmia, pericardial effusion, tamponade, constrictive pericarditis

# Pericardial Effusion

### Etiology
- transudative (serous)
- CHF, hypoalbuminemia/hypoproteinemia, hypothyroidism
- exudative (serosanguinous or bloody)
  - causes similar to the causes of acute pericarditis
  - may develop acute effusion secondary to hemopericardium (trauma, post-MI myocardial rupture, aortic dissection)
- physiologic consequences depend on type and volume of effusion, rate of effusion development, and underlying cardiac disease

### Signs and Symptoms
- may be asymptomatic or similar to acute pericarditis
- dyspnea, cough
- extra-cardiac (esophageal/recurrent laryngeal nerve/tracheo-bronchial/phrenic nerve irritation)
- JVP increased with dominant "x" descent
- arterial pulse normal to decreased volume, decreased pulse pressure
- auscultation: distant heart sounds ± rub
- Ewart's sign

**Ewart's Sign**
Bronchial breathing and dullness to percussion at the lower angle of the left scapula in pericardial effusion due to effusion compressing left lower lobe of lung

### Investigations
- ECG: low voltage, flat T waves, electrical alternans (classic, but not a sensitive sign to exclude effusion)
  - be cautious in diagnosing STEMI in a patient with pericarditis and an effusion – antiplatelets may precipitate hemorrhagic effusion
- CXR: cardiomegaly, rounded cardiac contour
- ER: bedside ultrasound with subxiphoid view showing fluid in pericardial sac
- Echo (procedure of choice): fluid in pericardial sac
- pericardiocentesis: definitive method of determining transudate vs. exudate, identify infectious agents, neoplastic involvement

### Treatment
- mild: frequent observation with serial echos, treat underlying cause, anti-inflammatory agents
- severe: treat as in tamponade (see *Cardiac Tamponade*)

# Cardiac Tamponade

### Etiology
- major complication of rapidly accumulating pericardial effusion
- cardiac tamponade is a clinical diagnosis
- any cause of pericarditis but especially trauma, malignancy, uremia, proximal aortic dissection with rupture

### Pathophysiology
- high intra-pericardial pressure → decreased venous return → decreased diastolic ventricular filling → decreased CO → hypotension and venous congestion

### Signs and Symptoms
- tachypnea, dyspnea, shock, muffled heart sounds
- pulsus paradoxus (inspiratory fall in systolic BP >10 mmHg during quiet breathing)
- JVP "x" descent only, blunted "y" descent
- hepatic congestion/peripheral edema

**Classic Quartet of Tamponade**
- Hypotension
- Increased JVP
- Tachycardia
- Pulsus paradoxus

### Investigations
- ECG: electrical alternans (pathognomonic variation in R wave amplitude), low voltage
- echo: pericardial effusion, compression of cardiac chambers (RA and RV) in diastole
- cardiac catheterization

**Beck's Triad**
- Hypotension
- Increased JVP
- Muffled heart sounds

### Treatment
- pericardiocentesis: Echo-guided
- pericardiotomy
- avoid diuretics and vasodilators (these decrease venous return to already under-filled RV → decrease LV preload → decrease CO) as well as mechanical ventilation
- IV fluid may increase CO
- treat underlying cause

# Constrictive Pericarditis

### Etiology
- chronic pericarditis resulting in fibrosed, thickened, adherent, and/or calcified pericardium
- any cause of acute pericarditis may result in chronic pericarditis
- major causes are idiopathic, post-infectious (viral, TB), radiation, post-cardiac surgery, uremia, MI, collagen vascular disease

### Signs and Symptoms
- dyspnea, fatigue, palpitations
- abdominal pain
- may mimic CHF (especially right-sided HF)
  - ascites, hepatosplenomegaly, edema
- increased JVP, Kussmaul's sign (paradoxical increase in JVP with inspiration), Friedreich's sign (prominent "y" descent)
- BP usually normal (and usually no pulsus paradoxus)
- precordial examination: ± pericardial knock (early diastolic sound)
- see Table 17 for differentiation from cardiac tamponade

**DDx Pulsus Paradoxus**
- Constrictive pericarditis (rarely)
- Severe obstructive pulmonary disease (e.g. asthma)
- Tension pneumothorax
- Pulmonary embolism (large)
- Cardiogenic shock
- Cardiac tamponade

### Investigations
- ECG: non-specific – low voltage, flat T wave, ± AFib
- CXR: pericardial calcification, effusions
- echo/CT/MRI: pericardial thickening, ± characteristic echo-Doppler findings
- cardiac catheterization: equalization of end-diastolic chamber pressures (diagnostic)

### Treatment
- medical: diuretics, salt restriction
- surgical: pericardiectomy (only if refractory to medical therapy)
- prognosis best with idiopathic or infectious cause and worst in post-radiation; death may result from heart failure

**Table 17. Differentiation of Constrictive Pericarditis vs. Cardiac Tamponade**

| Characteristic | Constrictive Pericarditis | Cardiac Tamponade |
|---|---|---|
| JVP | "y" > "x" | "x" > "y" |
| Kussmaul's sign | Present | Absent |
| Pulsus paradoxus | Uncommon | Always |
| Pericardial knock | Present | Absent |
| Hypotension | Variable | Severe |

# Common Medications

**Table 18. Commonly Used Cardiac Therapeutics**

| Drug Class | Examples | Mechanism of Action | Indications | Contraindications | Side Effects |
|---|---|---|---|---|---|
| **ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEI)** | | | | | |
| | enalapril (Vasotec®), perindopril (Coversyl®), ramipril (Altace®), lisinopril (Zestril®) | Inhibit ACE-mediated conversion of angiotensin I to angiotensin II (AT II), causing peripheral vasodilation and decreased aldosterone synthesis | HTN, CAD, CHF, post-MI, DM | Bilateral renal artery stenosis, pregnancy, caution in decreased GFR | Dry cough, 10% hypotension, fatigue, hyperkalemia, renal insufficiency, angioedema |
| **ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)** | | | | | |
| | candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan | Block AT II receptors, causing similar effects to ACEI | Same as ACEI, although evidence is generally less for ARBs; often used when ACEI are not tolerated | Same as ACEI | Similar to ACEI, but do not cause dry cough |
| **DIRECT RENIN INHIBITORS (DRIs)** | | | | | |
| | aliskiren | Directly blocks renin thus inhibiting the conversion of angiotensinogen to angiotensin I; this also causes a decrease in AT II | HTN (exact role of this drug remains unclear) | Pregnancy, severe renal impairment | Diarrhea, hyperkalemia (higher risk if used with an ACEI), rash, cough, angioedema, reflux, hypotension, rhabdomyolysis, seizure |
| **β-BLOCKERS** | | | | | |
| β1 antagonists<br><br>β1/β2 antagonists<br>α1/β1/β2 antagonists<br>β1 antagonists with intrinsic sympathomimetic activity | atenolol, metoprolol, bisoprolol<br>propranolol<br>labetalol, carvedilol<br>acebutalol | Block β-adrenergic receptors, decreasing HR, BP, contractility, and myocardial oxygen demand, slow conduction through the AV node | HTN, CAD, acute MI, post-MI, CHF (start low and go slow), AFib, SVT | Sinus bradycardia, 2nd or 3rd degree heart block, hypotension<br>Caution in asthma, claudication, Raynaud's phenomenon, and decompensated CHF | Hypotension, fatigue, light-headedness, depression, bradycardia, hyperkalemia, bronchospasm, impotence, depression of counterregulatory response to hypoglycemia, exacerbation of Raynaud's phenomenon, and claudication |
| **CALCIUM CHANNEL BLOCKERS (CCBs)** | | | | | |
| Benzothiazepines<br>Phenylalkylamines (non-dihydropyridines) | diltiazem<br>verapamil | Block smooth muscle and myocardial calcium channels causing effects similar to β-blockers<br>Also vasodilate | HTN, CAD, SVT, AFib, diastolic dysfunction | Sinus bradycardia, 2nd or 3rd degree heart block, hypotension, CHF | Hypotension, bradycardia, edema<br>Negative inotrope |
| Dihydropyridines | amlodipine (Norvasc®), nifedipine (Adalat®), felodipine (Plendil®) | Block smooth muscle calcium channels causing peripheral vasodilation | HTN, CAD | Severe aortic stenosis and liver failure | Hypotension, edema, flushing, headache, light-headedness |

**Table 18. Commonly Used Cardiac Therapeutics** (continued)

| Drug Class | Examples | Mechanism of Action | Indications | Contraindications | Side Effects |
|---|---|---|---|---|---|
| **DIURETICS** | | | | | |
| Thiazides | hydrochlorthiazide, chlorthalidone, metolazone | Reduce $Na^+$ reabsorption in the distal convoluted tubule (DCT) | HTN (drugs of choice for uncomplicated HTN) | Sulfa allergy, pregnancy | Hypotension, hypokalemia, polyuria |
| Loop diuretics | furosemide (Lasix®) | Blocks $Na^+/K^+$-ATPase in thick ascending limb of the loop of Henle | CHF, pulmonary or peripheral edema | Hypovolemia, hypokalemia | Hypovolemia, hypokalemic metabolic alkalosis |
| Aldosterone receptor antagonists | spironolactone, eplenerone | Antagonize aldosterone receptors | HTN, CHF, hypokalemia | Renal insufficiency, hyperkalemia, pregnancy | Edema, hyperkalemia, gynecomastia |
| **INOTROPES** | | | | | |
| | digoxin (Lanoxin®) | Inhibit $Na^+/K^+$-ATPase, leading to increased intracellular $Na^+$ and $Ca^{2+}$ concentration, and increased myocardial contractility<br>Also slows conduction through the AV node | CHF, AFib | 2nd or 3rd degree AV block, hypokalemia | AV block, junctional tachycardia, biderctional VT, bradyarrhythmias, blurred or yellow vision (van Gogh syndrome), anorexia, N/V |
| **ANTICOAGULANTS** | | | | | |
| Coumarins | warfarin (Coumadin®) | Antagonizes vitamin K, leading to decreased synthesis of clotting factors II, VII, IX, and X | AFib, LV dysfunction, prosthetic valves, venous thrombosis | Recent surgery or bleeding, bleeding diathesis, pregnancy | Bleeding (by far the most important side effect), paradoxical thrombosis, skin necrosis |
| Heparins | Unfractionated heparin<br>LMWHs: dalteparin, enoxaparin, tinzaparin | Antithrombin III agonist, leading to decreased clotting factor activity | Acute MI/ACS; when immediate anticoagulant effect needed, pulmonary embolism, venous thrombosis | Recent surgery or bleeding, bleeding diathesis, thrombocytopenia, renal insufficiency (for LMWHs) | Bleeding, osteoporosis, heparin-induced thrombocytopenia (less in LMWHs) |
| Direct thrombin inhibitors | dabigatran | Competitive, direct thrombin inhibitor; thrombin enables fibrinogen conversion to fibrin during the coagulation cascade, thereby preventing thrombus development | AFib, venous thrombosis, pulmonary embolism | Severe renal impairment, recent surgery, active bleeding | Bleeding, GI upset |
| Direct Factor Xa inhibitors | rivaroxaban<br>apixaban<br>edoxaban | Direct, selective and reversible inhibition of factor Xa in both the intrinsic and extrinsic coagulation pathways | AFib, venous thrombosis, pulmonary embolism | Hepatic disease, active bleeding, bleeding diathesis, pregnancy, lactation | Bleeding, elevated liver enzymes |
| **ANTIPLATELETS** | | | | | |
| Salicylates | ASA (Aspirin®) | Irreversibly acetylates platelet COX-1, preventing thromboxane A2-mediated platelet aggregation | CAD, acute MI, post-MI, post-PCI, CABG | Active bleeding or PUD | Bleeding, GI upset, GI ulceration, impaired renal perfusion |
| Thienopyridines | clopidogrel (Plavix®), ticlopidine (Ticlid®)<br>prasugrel (Effient®) | P2Y12 antagonist (block platelet ADP receptors) | Acute MI, post-MI, post-PCI, CABG | Active bleeding or PUD | Bleeding, thrombotic thrombocytopenic purpura, neutropenia (ticlopidine) |
| Nucleoside analogues | ticagrelor (Brillinta®) | P2Y12 antagonist (but different binding site than thienopyridines) | | | |
| GPIIb/IIIa inhibitors | eptifibatide, tirofiban, abciximab | Block binding of fibrinogen to Gp IIb/IIIa | Acute MI, particularly if PCI is planned | Recent surgery or bleeding, bleeding diathesis | Bleeding |
| **THROMBOLYTICS** | | | | | |
| | alteplase, reteplase, tenecteplase, streptokinase | Convert circulating plasminogen to plasmin, which lyses cross-linked fibrin | Acute STEMI | See Table 8, C29 | Bleeding |
| **NITRATES** | | | | | |
| | nitroglycerin | Relax vascular smooth muscle, producing venous and arteriolar dilation | CAD, MI, CHF (isosorbide dinitrate plus hydralazine) | Concurrent use of cGMP phosphodiesterase inhibitors, angle closure glaucoma, increased intracranial pressure | Headache, dizziness, weakness, postural hypotension |
| **LIPID LOWERING AGENTS** | | | | | |
| Statins | atorvastatin (Lipitor®), pravastatin (Pravachol®), rosuvastatin (Crestor®), simvastatin (Zocor®), lovastatin (Meracor®) | Inhibit HMG-CoA reductase, which catalyzes the rate-limiting step in cholesterol synthesis | Dyslipidemia (1° prevention of CAD), CAD, post-MI (2° prevention of CV events) | Liver or muscle disease | Myalgia, rhabdomyolysis, abdominal pain |
| Cholesterol absorption inhibitor | ezetimibe (Ezetrol®) | inhibits gut absorption of cholesterol | Decreases LDL but does not reduce mortality | Liver or renal impairment | Myalgia, rhabdomyolysis, abdominal pain |
| Miscellaneous | fibrates, bile acid sequestrates, nicotinic acid | | Primarily in familial hypercholesterolemia | | GI side effects common |
| PCKS9 inhibitor | evolocumab<br>alirocumab | monoclonal antibody | hypercholesterolemia | Hypersensitivity reaction to drug | Mild reactions to site of injection, nasopharyngitis |

# Antiarrhythmics

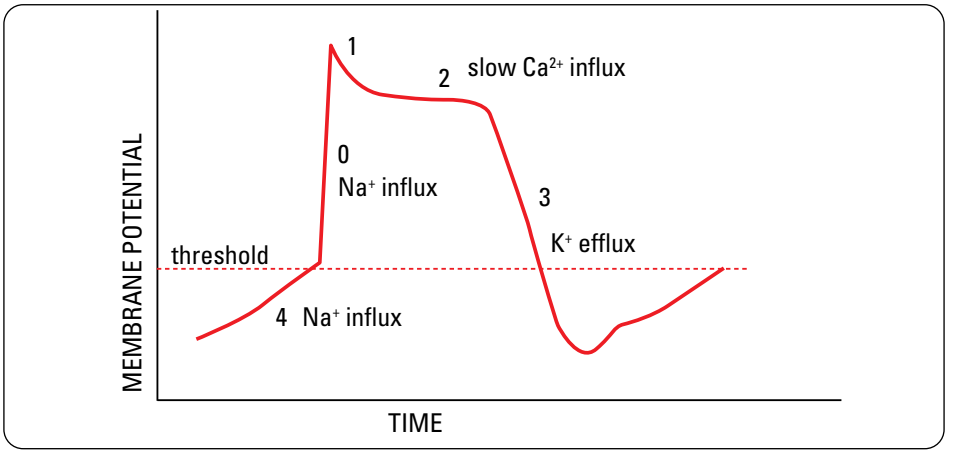



**Figure 46. Representative cardiac action potential**

**Table 19. Antiarrhythmic* Drugs (Vaughan-Williams Classification)**

| Class | Agent | Indications | Side Effects | Mechanism of Action |
|---|---|---|---|---|
| **Ia** | quinidine<br>procainamide<br>disopyramide | SVT, VT | Torsades de Pointes (all Ia), diarrhea<br>Lupus-like syndrome<br>Anticholinergic effects | Moderate $Na^+$ channel blockade<br>Slows phase 0 upstroke<br>Prolongs repolarization, slowing conduction |
| **Ib** | lidocaine<br>mexiletine | VT | Confusion, stupor, seizures<br>GI upset, tremor | Mild $Na^+$ channel blockade<br>Shortens phase 3 repolarization |
| **Ic** | propafenone<br>flecainide<br>encainide | SVT, VT<br>AFib | Exacerbation of VT (all Ic)<br>Negative inotropy (all Ic)<br>Bradycardia and heart block (all Ic) | Marked $Na^+$ channel blockade<br>Markedly slows phase 0 upstroke |
| **II** | propranolol<br>metoprolol, etc. | SVT, AFib | Bronchospasm, negative inotropy, bradycardia, AV block, impotence, fatigue | β-blocker<br>Decreases phase 4 depolarization |
| **III** | amiodarone**<br>sotalol | SVT, VT<br>AFib<br>SVT, VT, AFib | Amiodarone: Photosensitivity, pulmonary toxicity, hepatotoxicity, thyroid disease, increased INR<br>Amiodarone and Sotalol: Torsades de Pointes, bradycardia, heart block, β-blocker side effects | Blocks $K^+$ channel<br>Prolongs phase 3 repolarization, which prolongs refractory period |
| **IV** | verapamil<br>diltiazem | SVT<br>AFib | Bradycardia, AV block<br>Hypotension | Calcium channel blocker<br>Slows phase 4 spontaneous depolarization, slowing AV node conduction |

*All antiarrhythmics have potential to be proarrhythmic **Amiodarone has class I, II, III, and IV properties

**Table 20. Actions of α and β Adrenergic Receptors**

| | α RECEPTORS | | β RECEPTORS | |
|---|---|---|---|---|
| **Target System** | α1 | α2 | β1 | β2 |
| **Cardiovascular** | Constriction of vascular smooth muscle<br>Constriction of skin, skeletal muscle, and splanchnic vessels<br><br>Increased myocardial contractility<br>Decreased heart rate | Same as α1<br><br>Peripherally act to modulate vessel tone<br>Vasoconstrict and dilate; oppose α1 vasoconstrictor activity | Increased myocardial contractility<br>Accelerate SA node<br>Accelerate ectopic pacemakers | Decreased vascular smooth muscle tone |
| **Respiratory** | | | | Bronchodilation |
| **Dermal** | Pilomotor smooth muscle contraction<br>Apocrine constriction | | | |
| **Ocular** | Radial muscle contraction | | Ciliary muscle relaxation | |
| **Gastrointestinal** | Inhibition of myenteric plexus<br>Anal sphincter contraction | | | |
| **Genitourinary** | Pregnant uterine contraction<br>Penile and seminal vesicle ejaculation<br>Urinary bladder contraction | Smooth muscle wall relaxation | Stimulation of renal renin release | Bladder wall relaxation<br>Uterine relaxation |
| **Metabolic** | Stimulate liver gluconeogenesis and glycogenolysis at the liver | Same as α1<br>Fat cell lipolysis | Fat cell lipolysis<br>Glycogenolysis | Gluconeogenesis<br>Fat cell lipolysis |

Adapted from the Family Practice Notebook (www.fpnotebook.com/NEU194.htm)

**Table 21. Commonly Used Drugs that Act on α and β Adrenergic Receptors**

| | α RECEPTORS | | | β RECEPTORS | | |
|---|---|---|---|---|---|---|
| **Mechanism of Action** | α1 | α1 and α2 | α2 | β1 | β1 and β2 | β2 |
| **Agonist** | Phenylephrine<br>Methoxamine | Epinephrine<br>Norepinephrine | Clonidine<br>Methyldopa | Norepinephrine<br>Dobutamine | Isoproterenol<br>Epinephrine | Albuterol<br>Terbutaline |
| **Antagonist** | Prazosin<br>Phenoxybenzamine | Phentolamine | Yohimbine<br>Mirtazipine | Metoprolol<br>Acebutolol<br>Alprenolol<br>Atenolol<br>Esmolol | Propranolol<br>Timolol<br>Nadolol<br>Pindolol<br>Carvedilol | Butoxamine |

Adapted from the Family Practice Notebook (www.fpnotebook.com/NEU194.htm)

# Landmark Cardiac Trials

| Trial | Reference | Results |
|---|---|---|
| **ISCHEMIC HEART DISEASE** | | |
| ODYSSEY OUTCOMES | NEJM 2018;379:2097-2107 | Among patients with an ACS event within the preceding 1-12 mo, use of alirocumab, administered every other week, significantly reduces ischemic events, including all-cause mortality and MI |
| ARRIVE | Lancet 2018;392:1036-1046 | Among patients at moderate risk of CHD, the use of aspirin was not beneficial. Aspirin was not associated with a reduction in adverse cardiovascular events |
| ASCOT-LLA | Lancet 2003;361:1149-58 | In hypertensive patients with risk factors for CHD and average or below-average cholesterol, atorvastatin reduced nonfatal MI, fatal CHD, fatal/nonfatal stroke, coronary events but not all-cause mortality |
| CAPRIE | Lancet 1996;348:1329-39 | In atherosclerotic vascular disease, clopidogrel reduced the primary combined endpoint of stroke, MI, or vascular death and improved PAD compared to ASA |
| CARE | NEJM 1996;335:1001-9 | Pravastatin reduced MI and stroke in patients with previous MI and average cholesterol |
| COURAGE | NEJM 2007;356:1503-16 | Compared with optimal medical therapy alone, PCI + medical therapy did not reduce all-cause mortality and non fatal MI, and it did not reduce the incidence of major cardiovascular events |
| CURE | NEJM 2001;345:494-502 | Clopidogrel plus ASA reduced death from CV causes, non fatal MI, or stroke but increased bleeding complications |
| EUROPA | Lancet 2003;362:782-88 | With stable CAD and no CHF, perindopril reduced cardiovascular death, MI, and total mortality |
| HOPE | NEJM 2000;342:154-60 | In high-risk patients without low LVEF or CHF, ramipril reduced rates of death, MI, stroke, revascularization, new diagnosis of DM, and complications due to DM; vitamin E had no effect on outcomes |
| HPS | Lancet 2002;360:7-22 | In high-risk patients with various cholesterol values, simvastatin reduced all-cause mortality, coronary deaths, and major vascular events |
| INTERHEART | Lancet 2004;364:937-52 | Nine modifiable risk factors account for 90% of myocardial infarction |
| IMPROVE-IT | N Engl J Med 2015 Jun 18 | Ezetimibe added to statin reduces mortality in ACS patients |
| JUPITER | NEJM 2008;359:2195-2207 | With low to normal LDL-C and elevated hsCRP treatment with rosuvastatin significantly reduced major cardiovascular events; NNT with rosuvastatin for 2 yr to prevent one primary endpoint = 95 |
| SYNTAX | NEJM 2009;360:961-972 | CABG has lower rate of major cardiac or cerebrovascular events; the rate of stroke was increased with CABG, whereas the rate of repeat revascularization was increased with PCI |
| TNT | NEJM 2005;352:1425-35 | Lipid-lowering therapy with atorvastatin 80 mg/d in patients with stable CHD provides clinical benefit beyond atorvastatin 10 mg/d |
| WHI | JAMA 2002;288:321-333 | Estrogen plus progestin therapy is associated with increased risks of cardiovascular disease and breast cancer but decreased risks of hip fracture and colorectal cancer in postmenopausal women |

| Trial | Reference | Results |
|---|---|---|
| **MYOCARDIAL INFARCTION** | | |
| BHAT | JAMA 1982;247:1707-14 | In acute MI, propranolol reduced all-cause mortality, cardiovascular death, and sudden death from atherosclerotic heart disease |
| COURAGE | NEJM 2007;356:1503-16 | Compared with optimal medical therapy alone, PCI + medical therapy did not reduce all-cause mortality and non fatal MI, and it did not reduce the incidence of major cardiovascular events |
| DAPT | NEJM 2014;371:2155-66 | Dual antiplatelet therapy beyond one year confers additional benefit |
| ISIS-2 | Lancet 1988;2:349-60 | Early therapy with streptokinase and ASA in patients with MI individually and in combination significantly reduced all-cause mortality and in combination demonstrated additive effect |
| ISIS-4 | Lancet 1995;345:669-85 | In patients with suspected or definite acute MI, early treatment with captopril reduced all-cause mortality at 35 d and during long-term follow-up |
| OASIS-5 | NEJM 2006;354:1464-76 | Compared to enoxaparin, fondaparinux reduced mortality rates, major bleeds at 9 and MI at 30 and 180 d |
| PEGASUS-TIMI 54 | NEJM 2015;EPUB | Ticagrelor on top of ASA reduces CV events and in patients with a history of MI |
| PLATO | NEJM 2009:361:1045-57 | ACS patients with either STEMI or NSTEMI, regardless of reperfusion strategy, ticagrelor reduced mortality, MI, and stroke without increased bleeding compared to clopidogrel |
| PROVE IT – TIMI 22 | NEJM 2004;350:1495-1504 | In patients hospitalized for ACS, high-dose atorvastatin reduced all-cause mortality, MI, unstable angina, revascularization, and stroke compared with pravastatin |
| TRITON-TIMI 38 | NEJM 2007;357:2001-15 | In ACS patients scheduled for PCI, prasugrel reduced ischemic events but increased major bleeding compared to clopidogrel; no change in mortality |
| **HEART FAILURE** | | |
| PARTNER 3 | NEJM 2019;Epub ahead of print | Among low-risk patients with aortic stenosis, transcatheter aortic valve replacement (TAVR) was superior to surgical aortic valve replacement at preventing death, stroke, or rehospitalization at 1 year |
| COAPT | NEJM 2018;379:2307-2318 | Among patients with heart failure and moderate-to-severe or severe secondary mitral regurgitation who remained symptomatic despite the use of maximal doses of guideline-directed medical therapy, transcatheter mitral-valve repair resulted in a lower rate of hospitalization for heart failure and lower all-cause mortality within 24 mo of follow-up than medical therapy alone |
| AIRE | Lancet 1993;342:821-8 | Ramipril commenced 3-10 d after MI and continued for a mean 15 mo period significantly reduced all-cause mortality in patients with non-severe CHF |
| CHARM | Lancet 2003;362:759-66 | Candesartan reduced overall mortality, cardiovascular death, and CHF hospitalizations |
| CIBIS II | Lancet 1999;353:9-13 | Bisoprolol reduced all-cause mortality, cardiovascular death, all-cause hospitalization, and CHF hospitalization |
| COMET | Lancet 2003;362:7-13 | Carvedilol was associated with a reduction in all cause mortality compared with metoprolol |
| CONSENSUS | NEJM 1987;316:1429-35 | Enalapril reduced all-cause mortality, death due to progression of heart failure |
| COPERNICUS | NEJM 2001;344:1651-8 | Carvedilol in addition to standard treatment significantly reduced the risk of death or hospitalization in patients with severe CHF |
| I-PRESERVE | NEJM 2008;359:2456-2467 | In patients with CHF and normal LVEF treatment with ARB (irbesartan) did not improve mortality or cardiovascular morbidity compared to placebo |
| MERIT-HF | Lancet 1999;353:2001-7 | Metoprolol CR/XL daily in addition to optimum standard therapy improved survival in clinically stable patients equating to prevention of 1 death per 27 patients treated per year |
| PARADIGM-HF | NEJM 2014;371:993-1004 | Novel drug (LCZ696 containing valsartan and a neprilysin inhibitor (prevents degradation of natriuretic peptides) reduces hospitalization and mortality |
| RALES | NEJM 1999;341:709-17 | In severe CHF (class III/IV) and LVEF <35%, spironolactone reduced all-cause mortality, sudden death, and death due to progression of heart failure |
| SAVE | NEJM 1992;327:669-77 | Patients with LV dysfunction post-MI long-term captopril over 3.5 yr reduced the risk of death due to cardiovascular causes, recurrent MI, development of severe CHF, and CHF hospitalization |
| SCD-HeFT | NEJM 2005;352:225-237 | In mild-to-moderate CHF shock-only ICD significantly reduces risk of death; amiodarone had no benefit compared with placebo in treating patients with mild-to-moderate CHF |
| SOLVD | NEJM 1991;325:293-302 | In stable chronic CHF with decreased LVEF (<0.35), long-term enalapril reduced death due to all causes and death or hospitalization due to CHF |
| TRACE | NEJM 1995;333:1670-6 | In patients with LV dysfunction post-MI, long-term trandolapril reduced the risk of death or progression to severe CHF and reduced risk of sudden death |
| V-HeFT II | NEJM 1991;325:303-10 | In chronic CHF, enalapril reduced mortality more than hydralazine-isosorbide for at least 2 yr; treatment with either enalapril or hydralazine-isosorbide increased LVEF |

| Trial | Reference | Results |
|---|---|---|
| **DIABETES** | | |
| CARDS | Lancet 2004;264:685-96 | Atorvastatin reduces the risk of cardiovascular events in patients with type 2 DM |
| ONTARGET | NEJM 2008;358:1547-59 | In patients with vascular disease or DM without CHF, telmisartan is equally as effective as ramipril, with telmisartan causing a reduced risk of cough and angioedema, and an increased risk of hypotensive symptoms; combination therapy offers no advantage |
| **ARRHYTHMIA** | | |
| AFFIRM | NEJM 2002;347:1825-33 | No significant difference in mortality rates between rate or rhythm control of AFib |
| AF-CHF | NEJM 2008;358:2667-77 | In patients with AFib and CHF, there is no significant difference in mortality rates from cardiovascular causes between rate and rhythm control |
| ARISTOTLE | NEJM 2011;365:981-92 | AFib patients treated with apixaban had a lower incidence of stroke, major bleeding and mortality compared to warfarin |
| ENGAGE AF-TIMI48 | NEJM 2013;369:2093-2104 | AFib patients treated with edoxaban had similar rates of stroke and lower rates of major bleeding compared to warfarin |
| RE-LY | NEJM 2009;361:1139-51 | AFib patients treated with dabigatran had a lower incidence of stroke compared to warfarin, with similar rates of major bleeding |
| ROCKET-AF | NEJM 2011;365:883-891 | In patients with AFib rivoxabarin is non-inferior to warfarin for stroke prevention, and major and non-major bleeding |
| **HYPERTENSION** | | |
| HYVET | NEJM 2008;358:1887-98 | In hypertensive patients >80 yr treatment with indapamide, with or without perindopril, showed a trend towards reduced relative risk of fatal or non-fatal stroke |
| SIPLICITY-HTN 3 | NEJM 2014;370:1393-1401 | Renal denervation does not reduce blood pressure in patients with resistant hypertension compared to sham procedure |
| SPRINT | NEJM 2015;373:2103-2116 | In patients with high risk of cardiovascular events excluding diabetes, strict systolic BP control (<120 mmHg) is associated with fewer cardiovascular events and lower all-cause mortality |
| UKHDS (UKPDS) | BMJ 1998;317:703-13 | Hypertensive patients with DM and tight BP control at <150/85 mmHg by use of ACEI or β-blocker reduced risk of diabetic complications and death related to DM and reduced risk of end-organ damage |
| VALUE | Lancet 2004;363:2022-2031 | Valsartan group had higher incidence of MI than amlodipine group, whereas amlodipine had a higher incidence of new-onset DM |

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# CP Clinical Pharmacology

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# General Principles

## Drug Nomenclature

- **chemical name**: describes chemical structure; consistent in all countries via International Union of Applied Chemistry (e.g. N-(4-hydroxyphenyl)acetamide is acetaminophen)
- **DIN or NDC**: DIN assigned by Health Canada; NDC assigned by FDA (US)
- **non-proprietary name**: approved name (post-phase III trial), official name (listed in pharmacopeia), or generic name (off-patent) such as acetaminophen
- **proprietary (trade) name**: the brand name or registered trademark (e.g. Tylenol®)

## Phases of Clinical Drug Testing

- **pre-clinical**: testing a drug in a controlled environment (lab) on animal or human cells before human testing to discern the PK and toxicological profile
- **phase I**: first administration to healthy human volunteers, following animal studies; to determine PK and PD
- **phase II**: first administration to patients, small sample sizes; to determine initial safety and efficacy, dose range, PK, and PD
- **phase III**: double-blinded RCT; comparative (new drug vs. placebo or standard of care) to establish safety and efficacy
- **phase IV**: post-marketing surveillance, wide distribution; to determine effectiveness (in contrast to efficacy) and monitor long-term drug effects, and previously unappreciated ADRs

## Drug Administration

- choice of route of administration depends on: drug properties, local and systemic effects, desired time to onset and/or duration of action, and patient characteristics

**Table 1. Routes of Drug Administration**

| Route | Advantage | Potential Disadvantages |
|---|---|---|
| **Oral (PO)** | Convenient, easy to administer<br>Large surface area for absorption<br>Inexpensive relative to parenteral administration<br>Longer expiry date | Incomplete absorption<br>Hepatic first-pass effect<br>GI irritation<br>Higher likelihood of drug-drug interactions<br>Affected by dietary factors<br>Requires an intact GI system<br>Affected by GI motility |
| **Buccal/Sublingual (SL)** | Rapid onset of action<br>No hepatic first-pass effect | Must be lipid-soluble, non-irritating<br>Short duration of action |
| **Rectal (PR)** | Almost no hepatic first-pass effect<br>Use when NPO, vomiting, or unconscious | Inconvenient, irritation at site of application<br>Erratic absorption |
| **Intravenous (IV)** | No hepatic first-pass effect<br>Slow infusion or rapid onset of action<br>Easy to titrate dose | Hard to remove once administered<br>Risk of infection, bleeding, vascular injury, and extravasation<br>Expensive<br>Shorter expiry date |
| **Intramuscular (IM)** | Depot storage if oil-based = slow release of drug<br>Aqueous solution = rapid onset of action | Pain/hematoma at site of injection |
| **Subcutaneous (SC)** | Constant, even absorption<br>Alternative to IV<br>Easier administration (can be self-administered) | Pain at site of injection<br>Smaller volumes than IM<br>Possible tissue damage from multiple injections |
| **Intrathecal** | Direct into CSF<br>Bypass BBB and blood-CSF barrier | Risk of infection<br>Invasive procedure |
| **Inhalation** | Immediate action in lungs<br>Rapid delivery to blood<br>No hepatic first-pass effect | Must be gas, vapour, or aerosol |
| **Topical (skin, mucous membranes, eyes)** | Easy to administer<br>Localized (limited systemic absorption) | Effects are mainly limited to site of application |
| **Transdermal** | Drug absorption through intact skin<br>No hepatic first-pass effect | Irritation at site of application<br>Delayed onset of action<br>Hydrophilic drugs not easily absorbed |
| **Others (Intraperitoneal, Intra-Articular)** | Local effect | Risk of infection |

# Acronyms

| | |
|---|---|
| ACE | angiotensin converting enzyme |
| ACh | acetylcholine |
| ADE | adverse drug event |
| ADR | adverse drug reaction |
| ARB | angiotensin receptor blocker |
| AUC | area under the concentration-time curve |
| BBB | blood brain barrier |
| Cl | clearance |
| Cr | creatinine |
| CSF | cerebrospinal fluid |
| CSFa | certain safety factor |
| CYP | cytochrome P450 enzyme |
| DIN | drug identification number |
| F | bioavailability |
| FDA | Food and Drug Administration |
| GFR | glomerular filtration rate |
| HH | Henderson-Hasselbalch |
| NDC | National Drug Code |
| NE | norepinephrine |
| NPO | nothing by mouth |
| Po/w | partition coefficient of a drug |
| PD | pharmacodynamics |
| PDE | phosphodiesterase |
| P-gp | P-glycoprotein |
| PK | pharmacokinetics |
| RCT | randomized controlled trial |
| TBW | total body water |
| TDM | therapeutic drug monitoring |
| TI | therapeutic index |
| Vd | volume of distribution |



At the time of drug launch, only data from phases I-III are available; thus, effectiveness and safety may be unknown because real-world patients and usage patterns often differ from those in premarket phases



**Common Latin Abbreviations**

| | |
|---|---|
| q | each, every |
| OD/bid/tid/qid | once/twice/three/four times a day |
| hs | at bedtime |
| ac/pc/cc | before/after/with meals |
| prn | as necessary |
| gtt | drops |
| ung | ointment |
| ud | as directed |
| od/os/ou | right/left/each eye |
| ad/as/au | right/left/each ear |

NOTE: Certain abbreviations, symbols, and dose designations may contribute to medication errors. For more information, refer to guidelines by the Institute for Safe Medication Practices (ISMP)

# Pharmacokinetics

- study of "what the body does to a drug" – i.e. the fate of a drug following administration
- **definition**: relationship between drug administration, time-course/rate of absorption and distribution, concentration changes in the body compartments, and the drug's removal from the body

## Absorption

- **definition**: movement of the drug from the site of administration into plasma

### Mechanisms of Drug Absorption

- most drugs are absorbed into the systemic circulation via passive diffusion
- other mechanisms include active transport, facilitated diffusion, and pinocytosis/phagocytosis

### Factors Affecting the Rate and Extent of Drug Absorption

- $P_{o/w}$
- local blood flow at the site of administration (e.g. sublingual vessels facilitate rapid absorption of sublingually-administered medications)
- molecular size (e.g. drugs with smaller molecular weight are absorbed faster)
- pH and drug ionization
  - drugs are usually weak acids (e.g. ASA) or weak bases (e.g. ketoconazole) and thus exist in ionized and non-ionized forms
  - non-ionized forms cross cell membranes more readily than ionized (charged) forms
  - the ratio of ionized to non-ionized forms is determined by body compartment pH and drug pKa (H-H equation)
- total surface area for absorption
  - small intestinal villi are the primary site of absorption for most oral drugs

**$P_{o/w}$**
- Ratio of a drug's solubility in oil/lipid (e.g. cell membrane) as compared to water (e.g. extracellular fluid)
- A large $P_{o/w}$ (e.g. anesthetics) means that a drug is highly soluble in lipid and will cross cell membranes easily

### Bioavailability (F)

- **definition**: proportion of dose that reaches systemic circulation in an unchanged state
- lower F usually reflects limited drug absorption or first-pass effect
- IV dose has 100% bioavailability (F = 1)

### First-Pass Effect

- **definition**: drug metabolism by the liver and/or the gut before it reaches systemic circulation, resulting in reduced F
- occurs with PO administration of a drug: GI tract (absorption) → portal vein to liver (first-pass metabolism) → systemic circulation
- 50% of the PR administered drug absorbed in colon bypasses the portal system. CYP3A4 in the enterocytes reduce the bioavailability of some rectally administered medications

**Examples of Drugs with High First-Pass Effect**
- Levodopa
- Morphine
- Propranolol
- Lidocaine
- Organic nitrates
- Simvastatin

**Examples of Drugs with Low First-Pass Effect**
- Diazepam
- Digoxin
- Phenytoin
- Warfarin

### Efflux Pump

- P-gp is a protein found in various parts of the body that acts as a multidrug efflux pump involved in the transport of drugs out of cells
- for example, P-gp opposes intestinal absorption (e.g. dabigatran etexilate) and also enhances renal elimination of certain drugs (e.g. digoxin, etoposide, paclitaxel, tacrolimus, cyclosporine)
- some drugs (e.g. macrolide antibiotics) inhibit P-gp function, leading to increased serum concentrations of drugs transported by P-gp; P-gp inducers (e.g. rifampin, St. John's wort) do the opposite
- some tumours overexpress P-gp leading to multidrug resistance to chemotherapeutic agents

## Distribution

- **definition**: movement of drugs between different body compartments and to the site of action
- major body fluid compartments include plasma, interstitial fluid, intracellular fluid, transcellular fluid (e.g. CSF, peritoneal, pleural)
- tissue compartments include fat, brain

### Factors Affecting the Rate and Extent of Drug Distribution

- physiochemical properties of the drug (e.g. $P_{o/w}$ and pKa)
- pH of fluid
- plasma protein binding
- binding within compartments (i.e. depots)
- regional blood flow

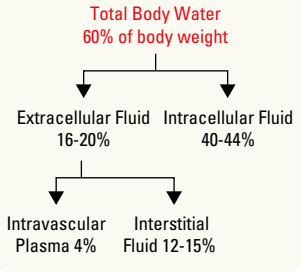



**Figure 1. Distribution of total body water (TBW)**

### Volume of Distribution

- $V_d$: the apparent volume of fluid into which a drug distributes
- maximum actual $V_d$ (anatomic fluid volume accessible to drug) = TBW (~40 L for average adult)
  - a calculated value ($V_d$) = amount of drug in body ÷ plasma drug concentration
  - a theoretical value that does not correspond to an anatomical space (i.e. can exceed TBW)
  - small $V_d$ corresponds to a drug that concentrates in plasma and/or binds plasma proteins to a high degree
  - large $V_d$ corresponds to a drug that distributes into tissues (fat, muscle, etc.); most is not in blood (measured) space; it therefore "appears" to distribute in a large volume
  - $V_d$ of plasma protein bound drugs can be altered by liver and kidney disease
  - $V_d$ of drugs change with age
    - in geriatric populations, there is a reduction in total body water and total muscle mass, but an increase in total body fat resulting in an increase in the $V_d$ of lipophilic drugs
    - $V_d$ of drugs will change in the geriatric population based on the drug $P_{o/w}$
- example: amiodarone distributes into TBW (actual $V_d$ ~40 L), but it concentrates in fat tissues yielding an apparent $V_d$ of 400 L; therefore, to achieve a given plasma concentration of amiodarone, we dose as though the drug distributes into 400 L of body fluid



Multiple drugs and endogenous substances can compete for the same protein binding sites. For example, ASA displaces highly protein-bound acidic drugs such as phenytoin, thus increasing risk of toxicity, and sulfonamide displaces bilirubin, which could potentially lead to jaundice and kernicterus in neonates

### Plasma Protein Binding

- drug molecules in the blood exist in an equilibrium of two forms:
  1. bound to plasma protein: acidic drugs bind to albumin, basic drugs bind to α1-acid glycoprotein
  2. free or unbound: can leave the circulation to distribute into tissues and exert an effect, subject to metabolism and elimination
- bound fraction is determined by drug concentration, binding affinity, and plasma protein concentration (number of binding sites)
- reduced number of binding sites (e.g. hypoalbuminemia) or saturation of binding sites (e.g. competition/displacement) may result in increased concentration of free drug, which is often metabolized with no harmful effects, although toxicity is possible



Special consideration must be given in dosing patients in hypoalbuminemic states (e.g. liver failure or nephrotic syndrome) to prevent drug toxicity. Highly protein-bound drugs (e.g. warfarin, digoxin, diazepam, furosemide, amitriptyline) will exert a greater effect in these patients than in healthy individuals because of higher levels of free drug

### Depots

- a body compartment in which drug molecules tend to be stored and released slowly over a long period of time
- fat is a depot for very lipid soluble drugs (e.g. diazepam)
- some oil-based medications are injected IM for slow release (e.g. depot medroxyprogesterone acetate q3mo; depot risperidone q2wk)

### Barriers (relative)

- body structures that limit or prevent diffusion of drug molecules, such as the placenta or BBB (a barrier composed of tight junctions between capillary endothelial cells and astrocytes)
- many of these barriers result, in part, from the activity of multidrug efflux pumps (e.g. P-gp), which serve as a natural defense mechanism against drugs and xenobiotics
- need to consider dosing route if drugs are meant to cross these barriers
- barriers are important in determining site of action and side effects profile of drugs (e.g. CNS depression if drug crosses BBB, risk of harm to a fetus if drug crosses placental barrier)



**Main Factors Governing Penetration of BBB**

- Small molecular size (<500 Da)
- High lipid solubility
- Active transport mechanisms (e.g. Pgp efflux pump)

## Metabolism (Biotransformation)

- **definition**: chemical transformation of a drug *in vivo*
- sites of biotransformation include liver (main), GI tract, lung, plasma, kidney
- as a result of the process of biotransformation:
  - an inactive prodrug may be **activated** (e.g. tamoxifen to endoxifen; codeine to morphine)
  - a drug may be **changed** to another active metabolite (e.g. diazepam to oxazepam and others)
  - a drug may be **changed** to a toxic metabolite (e.g. meperidine to normeperidine)
  - a drug may be **inactivated** (most drugs)

### Drug Metabolizing Pathways

- **phase I (P450) reactions**
  - minor molecular changes introduce or unmask polar groups on a parent compound to increase water solubility (e.g. oxidation-reduction, hydrolysis, hydroxylation, demethylation); the change in $P_{o/w}$ is typically minimal compared to phase II, and often phase I places a polar 'handle' on a lipophilic drug to allow for phase II
  - mediated by CYPs found in the endoplasmic reticulum (primarily in hepatocytes)
  - product of the reaction can be excreted or undergo further phase II reactions
- **phase II (conjugation) reactions**
  - conjugation with large polar endogenous substrates (e.g. glucuronidation, glutathione conjugation, sulfation)
  - dramatically increases water solubility and renal elimination
  - can result in biologically active metabolites (e.g. glucuronides of morphine)
  - can occur independently of phase I reactions

### Factors Affecting Drug Biotransformation

- **genetic polymorphisms** of metabolizing enzymes
  - for some enzymes, individual genotypes may alter the rate of drug metabolism (e.g. poor, intermediate, extensive, or ultrarapid metabolizers)
  - may lead to toxicity or ineffectiveness of a drug at a normal dose
  - tamoxifen and codeine are prodrugs activated by CYP2D6 (nonfunctional alleles reduce effectiveness, whereas duplicated alleles impart "ultra-rapid metabolizer" phenotype)
  - warfarin is metabolized by CYP2C9 (nonfunctional alleles lead to greater effect and lower dose requirements)
- **enzyme inhibition** may sometimes be due to other drugs
  - CYP inhibition leads to an increased concentration and bioavailability of the substrate drug (e.g. erythromycin [CYP3A4 inhibitor] can predispose patients to simvastatin toxicity [metabolized by CYP3A4])
  - grapefruit juice is a potent inhibitor of intestinal CYP3A4, resulting in numerous drug interactions (e.g. saquinavir AUC increased 3-fold, simvastatin 17-fold)
- **enzyme induction**
  - certain medications enhance gene transcription leading to an increase in the activity of a metabolizing enzyme
  - a drug may induce its own metabolism (e.g. carbamazepine) or that of other drugs (e.g. phenobarbital can induce the metabolism of OCPs) by inducing the CYP system
- **liver dysfunction** (e.g. hepatitis, alcoholic liver, biliary cirrhosis, or hepatocellular carcinoma) may decrease drug metabolism but this may not be clinically significant due to the liver's reserve capacity
- **renal disease** often results in decreased drug clearance
- **extremes of age** (neonates or elderly) have reduced biotransformation capacity, and doses should be adjusted accordingly
- **nutrition**: insufficient protein and fatty acid intake decreases CYP biotransformation, and vitamin/mineral deficiencies may also impact other metabolizing enzymes
- **alcohol**: while acute alcohol ingestion inhibits CYP2E1, chronic consumption can induce CYP2E1 and increase risk of hepatocellular damage from acetaminophen by increasing the production of acetaminophen's toxic metabolite (NAPQI)
- **smoking** can induce CYP1A2, thus increasing the metabolism of some drugs (e.g. theophylline, antipsychotics)



**Cytochrome P450 System**
The CYPs are a superfamily of heme proteins that are grouped into families and subfamilies according to their amino acid sequence. These proteins are responsible for the metabolism of drugs, chemicals, and other substances

Nomenclature: CYP3A4
"CYP" = cytochrome P450 protein
1st number = family
letter = subfamily
2nd number = isoform

The CYP1, CYP2, and CYP3 families metabolize most drugs in humans. The most important isoforms are CYP3A4 and CYP2D6; therefore, anticipate drug interactions if prescribing drugs using these enzymes



**Examples of CYP Substrates, Inhibitors, and Inducers**
http://www.medicine.iupui.edu/CLINPHARM/ddis/main-table

## Elimination

- **definition**: removal of drug from the body

### Routes of Drug Elimination

- **kidney** (main organ of elimination)
  - renal drug clearance = (glomerular filtration + tubular secretion) – (tubular reabsorption)
  - two mechanisms:
    1. **glomerular filtration**
       – a passive process, so that only the free drug fraction can be eliminated
       – drug filtration rate depends on GFR, degree of protein binding of drug, and size of drug
    2. **tubular secretion**
       – an active process that is saturable allowing both protein-bound and free drug fractions to be excreted
       – distinct transport mechanisms for weak acids (e.g. penicillin, salicylic acid, probenecid, chlorothiazide) and weak bases (e.g. quinine, quaternary ammonium compounds such as choline)
       – drugs may competitively block mutual secretion if both use the same secretion system (e.g. probenecid can reduce the excretion of penicillin)
- **tubular reabsorption**: drugs can be actively or passively reabsorbed back to the systemic circulation, countering elimination mechanisms
- **renal function** (assessed using serum Cr levels) decreases with age (7.5 mL/min per decade) and is affected by many disease states such as diabetes
- **stool**: some drugs and metabolites are actively excreted in the bile or directly into the GI tract
  - enterohepatic reabsorption counteracts stool elimination, and can prolong the drug's duration in the body
  - some glucuronic acid conjugates that are excreted in bile may be hydrolyzed in the intestines by bacteria back to their original form and can be systemically reabsorbed
- **lungs**: elimination of anesthetic gases and vapours by exhalation
- **saliva**: saliva concentrations of some drugs parallel their plasma concentrations (e.g. rifampin)



**The Cockcroft-Gault Equation can Estimate CrCl in Adults 20 yr of Age and Older**

- For males

$$\text{CrCl (mL/min)} = \frac{[(140 - \text{age in yr}) \times \text{Weight (kg)}] \times 1.2}{\text{serum Cr (μmol/L)}}$$

- For females, multiply above equation x 0.85
- Use ideal body weight in obese patients

**Limitations of Cockroft-Gault Equation**

- In individuals with large muscle mass, the equation underestimates renal clearance
- In the elderly population, physiological loss of muscle mass may result in overestimation of renal clearance

Note, only applies when renal function is at steady state



Avoid toxicity from drug or metabolite accumulation by adjusting a drug's dosage according to the elimination characteristics of the patient

# Pharmacokinetic Calculation

- **definition**: the quantitative description of the various steps of drug disposition (i.e. how drugs move through the body)
- the pharmacokinetic principles of ADME (absorption, distribution, metabolism, and elimination) can be graphically represented on a graph of concentration vs. time

## Time Course of Drug Action

- many kinetic parameters are measured using IV dosing, such that absorption is immediate and distribution for most drugs is rapid; thus elimination is the main process being measured
- the concentration axis is converted to a log10 concentration to allow for easier mathematical calculations
- drugs such as warfarin can exhibit hysteresis (for a single drug concentration, there may be two different response levels)

## Half-Life

- **definition**: time taken for the serum drug level to fall 50% during elimination
- drugs with first order kinetics require five half-lives to reach steady state with repeated dosing or for complete drug elimination once dosing is stopped

## Steady State

- drug concentration remains constant when amount of drug entering the system is the same as the amount eliminated from the system
- drug levels in therapeutic drug monitoring are of greatest utility when the steady state has been reached
- special situations
  - use a loading dose for drugs with a long half-life and when there is clinical need to rapidly achieve therapeutic levels (e.g. amiodarone, digoxin, phenytoin)
  - use continuous infusion for drugs with a very short half-life and when there is need for a long-term effect and multiple or frequently repeated doses are too inconvenient (e.g. nitroprusside, unfractionated heparin, naloxone)

## Clearance

- a quantitative measurement of the body fluid volume from which a substance is removed per unit time
- Cl = rate of elimination of drug ÷ plasma drug concentration
- must consider Cl from a specific part of the body and total body Cl

## Elimination Kinetics

- first-order kinetics (most common type)
  - constant fraction of drug eliminated per unit time
  - some drugs can follow first-order kinetics until elimination is saturated (usually at large doses) at which point the Cl is less than would be predicted for a given concentration
  - shows linear relationship when plotted on a graph of concentration (log) vs. time (linear)
- zero-order kinetics (less common, associated with overdose, e.g. alcohol)
  - constant amount of drug eliminated per unit time, regardless of concentration; concept of half-life does not apply
  - the concentration axis is converted to a log (concentration) to allow for easier mathematical calculations
- non-linear kinetics (much less common)
  - unlike first-order kinetics which assumes no change in PK parameter with drug dose, non-linear kinetics is considered dose-dependent
  - saturation of various ADME processes creates non-linear kinetics
  - the complexity of dosing drugs with non-linear kinetics has resulted in creation of drug-specific nomograms to aid clinicians in dosing, with these drugs often being the target of therapeutic drug monitoring
    - examples: phenytoin, theophylline

## Loading and Maintenance Doses

- loading doses are used when immediate effect is needed with parenteral administration being the most common way of giving a large dose to "fill up" the volume of distribution
- maintenance doses are given after a loading dose OR drug regimen can begin with maintenance doses
  - steady state levels are achieved after ~5 half lives
  - can be given as either a continuous infusion (rare) or more commonly as intermittent oral doses

# Pharmacodynamics

- study of "what the drug does to the body"

## Dose-Response Relationship

- graded dose-response relationships: relates dose to intensity of effect

## Efficacy

- the maximum biological response produced by a drug
- measured by $E_{max}$ (the maximal response that a drug can elicit in a RCT or under optimal circumstances)

## Potency

- measured by $EC_{50}$ (the concentration of a drug needed to produce 50% of $E_{max}$)
- a drug that reaches its $EC_{50}$ at a lower dose is more potent

**Efficacy vs. Potency**

- Efficacy measures the maximal effect of a drug
- Potency measures the concentration of a drug needed to produce a certain effect

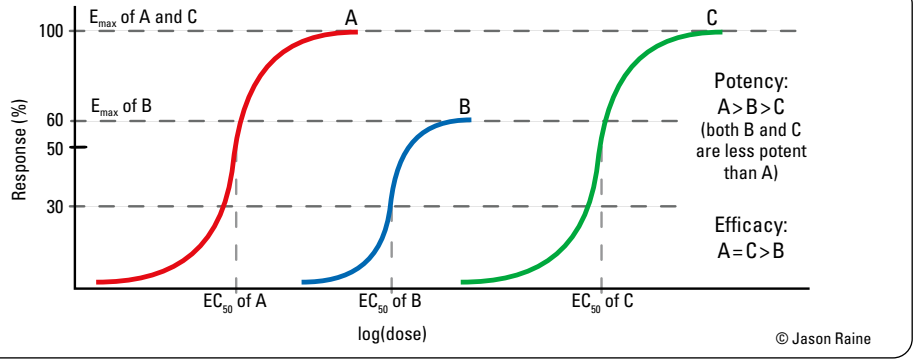
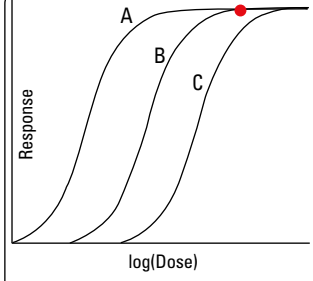
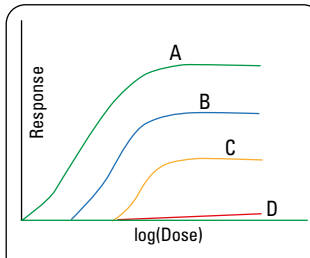



**Figure 2. Log(dose)-response curve illustrating efficacy and potency**




A → C increasing dose of competitive antagonist
At each dose of antagonist, increasing the concentration of agonist can overcome the inhibition

**Figure 3. The log(dose)-response curve for competitive reversible antagonism**




A → D increasing dose of irreversible antagonist. With co-administration of antagonist, increasing dose of agonist does not completely overcome antagonism, as seen in B. Eventually with high enough antagonism concentrations, no amount of agonist can elicit a response, as seen in D

**Figure 4. The log(dose)-response curve for irreversible antagonism**

# Effects of Drugs on Receptors

## Agonists

- drugs that mimic the effects of the endogenous ligand and evoke a response when bound to the receptor
  - **affinity**: the ability of the agonist to bind to the receptor (e.g. the β2-agonist salbutamol has greater affinity for β2-receptors than β1-receptors)
  - **efficacy**: the ability to recapitulate endogenous response via the receptor interaction (e.g. binding of salbutamol to β2-receptors results in smooth muscle relaxation)
    - drug efficacy in an RCT is different than efficacy in the context of pharmacological principles
- **full agonists**: can elicit a maximal effect at a receptor (e.g. methadone and morphine on the μ opioid receptor system)
- **partial agonists**: can only elicit a partial effect, no matter the concentration at the receptor (i.e. reduced efficacy compared to full agonists) (e.g. buprenorphine on the μ opioid receptor system)

## Antagonists

- drugs that reduce the action of an agonist or of an endogenous ligand
- **chemical antagonism**: direct chemical interaction between agonist and antagonist prevents agonist-receptor binding (e.g. chelating agents for removal of heavy metals)
- **physiological/functional antagonism**: two agonists that act independently at different receptors and have opposite physiological effects (e.g. acetylcholine at the muscarinic receptor compared to epinephrine at the adrenergic receptor)
- **pharmacological antagonism**: antagonist inhibits agonist through acting on receptor or alternative effector site
- **reversible and irreversible competitive antagonism**
  - drugs that exert no direct effect upon binding to a given receptor (i.e. zero efficacy)
  - reversible competitive antagonists reversibly bind to the same receptor as the agonist, thus displacing it (e.g. naloxone is an antagonist to morphine or heroin)
  - irreversible antagonists form a covalent bond with the receptor, thus irreversibly blocking substrates from binding (e.g. phenoxybenzamine forms a covalent bond with adrenergic receptors preventing adrenaline and NE from binding)
- **non-competitive antagonism**
  - antagonist binds to an alternate site near the agonist site, producing allosteric effects that change the ability of the agonist to bind (e.g. organophosphates irreversibly bind acetylcholinesterase)

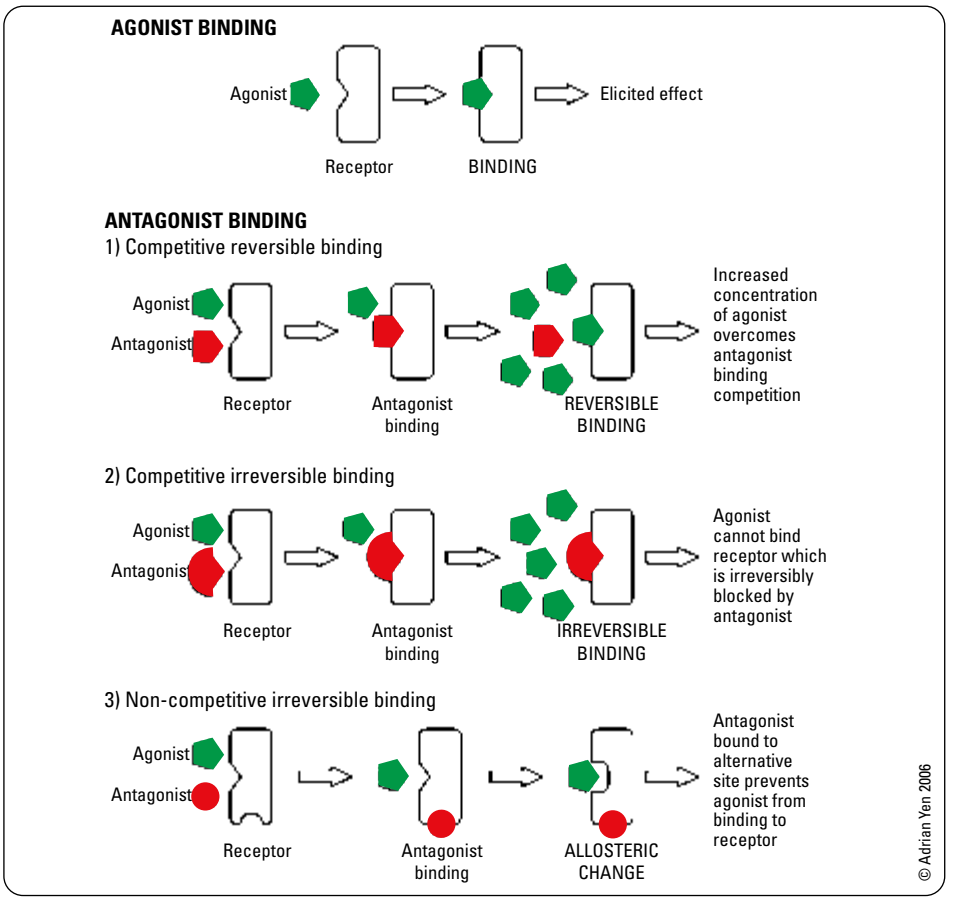



**Figure 5. Mechanism of agonists and antagonists**

# Effectiveness and Safety

### Effectiveness

- $ED_{50}$ (effective dose): the dose of a drug needed to cause a therapeutic effect in 50% of a test population of subjects

### Safety

- $LD_{50}$ (lethal dose): the dose of a drug needed to cause death in 50% of a test population of subjects
- $TD_{50}$ (toxic dose): the dose needed to cause a harmful effect in 50% of a test population of subjects

The two most clinically relevant properties of any drug are effectiveness and safety

# Therapeutic Indices

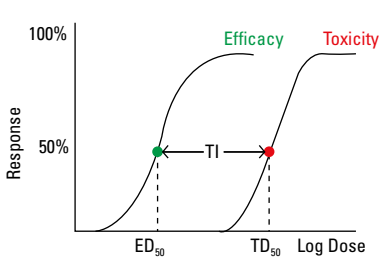
### Therapeutic Index: $TD_{50}/ED_{50}$

- reflects the "margin of safety" for a drug – the likelihood of a therapeutic dose to cause serious toxicity or death
- the larger the TI, the safer a drug
- common drugs with a narrow TI that require therapeutic drug monitoring include: digoxin, theophylline, warfarin, lithium, and cyclosporine
- factors that can change the TI
  - presence of interacting drugs
  - changes in drug ADME

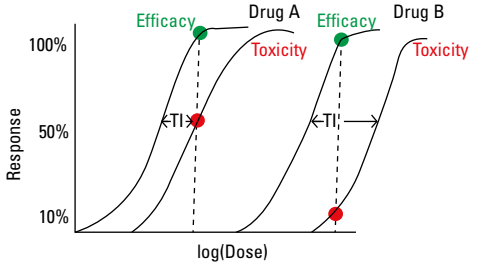
Drugs with a narrow TI have a high likelihood of causing toxicity and need close therapeutic monitoring

### Certain Safety Factor: $TD_1/ED_{99}$

- >1 translates to a dose effective in at least 99% of the population and toxic in less than 1% of the population




The therapeutic index ($TD_{50}/ED_{50}$) is a measure of the margin of safety of a given drug




Drug A has a much narrower therapeutic index than Drug B. The dose of Drug A required to achieve a 100% therapeutic response will be toxic in 50% of patients. For Drug B, this is only 10%

**Figure 6. $ED_{50}$, $TD_{50}$, and the therapeutic index**

# Therapeutic Drug Monitoring

- **definition**: using serum drug concentration data to optimize drug therapy (e.g. dose adjustment, monitor compliance) serum drug samples are usually taken when the drug has reached steady state (after approximately 5 half-lives)
- TDM is often used for drugs that have: narrow TIs, unpredictable dose-response relationships, significant consequences associated with therapeutic failure or toxicity, and wide inter-patient PK variability
- nomograms are often used for narrow TI drugs, particularly in the setting of patients with complex clinical factors such as renal insufficiency, hepatic failure, dialysis, hypoalbuminemia
- examples of drugs that require therapeutic drug monitoring include:
  - vancomycin
  - aminoglycosides (gentamicin, tobramycin)
  - digoxin
  - phenytoin and other anticonvulsants
  - warfarin
  - lithium

# Adverse Drug Reactions

- adverse drug events (ADEs) are events that occur while a patient is on a drug at either appropriate or inappropriate doses. A causal relationship is not required
- adverse drug reactions (ADRs) are reactions to drugs that occur when a drug is used for the appropriate indication at normal therapeutic doses

**Table 2. Characteristics of Type A-E Adverse Drug Reactions**

| Classification | Definition | Characteristics |
|---|---|---|
| **A (Augmented)** | Dose related | Predictable extension of drug's pharmacologic effect (e.g. β-blockers causing bradycardia)<br>>80% of all ADRs |
| **B (Bizarre)** | Non-dose related | Reactions unrelated to the known pharmacological actions of the drug<br>Examples include: drug hypersensitivity syndromes, immunologic reactions (penicillin hypersensitivity), and idiosyncratic reactions (malignant hyperthermia) |
| **C (Chronic)** | Dose and time related | Related to cumulative doses<br>Effects are well-known and can be anticipated (e.g. atypical femoral fracture from bisphosphonates) |
| **D (Delayed)** | Time related | Occurs some time after use of drug (e.g. carcinogen)<br>May also be dose-related |
| **E (End of use)** | Withdrawal | Occurs after cessation of drug use (e.g. opiate withdrawal) |



**Tips to Reduce Drug-Related Adverse Events in the Elderly**

- Be mindful of longstanding medications that have never been adjusted for patient age or renal or hepatic function
- Consider whether medications initiated during hospital admission are needed long-term (and whether the discharge dose is appropriate for maintenance)
- Avoid polypharmacy by decreasing the dose of or discontinuing medications that are causing side effects
- Verify adherence to medications before automatically increasing the dose of subtherapeutic treatment
- When prescribing medications, use those with a wide therapeutic window
- Review the patient's problem list and reconcile current medications to avoid duplication or inappropriate dosing/frequency

# Approach to Suspected Adverse Drug Reactions

- history and physical exam: signs and symptoms of reaction (e.g. rash, fever, hepatitis, anaphylaxis), timing, risk factors, detailed medication history including all drugs and timing, de-challenge (response when drug is removed), and re-challenge (response when drug is given again, if applicable)
- differentiate between drug therapy vs. disease pathophysiology
- treatment: stop the drug, supportive care, symptomatic relief. Specific interventions (eg. steroids, immunosuppressants) used for some ADRs
- resources: check recent literature, Health Canada, and FDA; contact the pharmaceutical company; call Poison Control (1-888-268-9017) if overdose or poisoning suspected; check with MotherToBaby (https://mothertobaby.org/) in cases involving pregnant or breastfeeding women
- report all suspected ADRs that are: 1) unexpected, 2) serious, or 3) reactions to recently marketed drugs (on the market <5 yr) regardless of nature or severity
  - Canadian Adverse Drug Reaction Monitoring Program available for online reporting

# Variability in Drug Response

- recommended patient dosing is based on clinical research and represents mean values for a select population, but each person may be unique in their dosing requirements
- possible causes of individual variability in drug response include problems with:
  - intake: patient adherence
  - PK
  - absorption: vomiting, diarrhea, or steatorrhea; first pass effect increased due to enzyme induction or decreased due to liver disease
  - drug interactions (e.g. calcium carbonate complexes with iron, thyroxine, and fluoroquinolones)
  - distribution: very high or low percentage body fat; intact or disrupted BBB; patient is elderly or a neonate, or has liver dysfunction
  - biotransformation and elimination: certain genetic polymorphisms or enzyme deficiencies related to drug metabolism (e.g. acetylcholinesterase deficiency, CYP polymorphism); kidney or liver dysfunction
  - PD: genetic variability in drug response (e.g. immune-mediated reactions); diseases that affect drug PD; drug tolerance or cross-tolerance

# Drug Interactions

- concomitant prescriptions: one drug alters the effect of another by changing its PK and/or PD
- PK interactions involve changes in drug concentration
  - absorption: alterations in gastrointestinal pH, gastric emptying, intestinal motility, gut transporters
  - metabolism: alterations in drug metabolizing enzymes (e.g. CYP)
  - excretion: alterations in renal elimination
- PD interactions are due to two drugs that exert similar effects (additive) or opposing effects (subtractive)
- drug interactions can also involve herbal medications (e.g. St. John's wort) and food (e.g. grapefruit juice)

# Autonomic Pharmacology

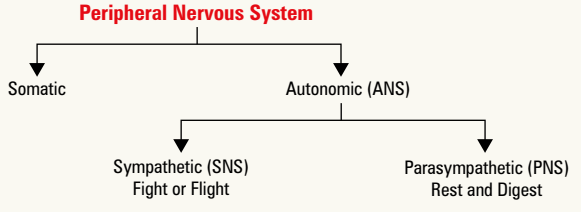



**Figure 7. Subdivisions of the peripheral nervous system**

- most organs are innervated by both sympathetic and parasympathetic nerves, which have opposing effects (see Neurology, N8)
- ACh and NE are the main neurotransmitters of the autonomic NS
- ACh binds to cholinergic receptors, which include nicotinic and muscarinic receptors
- NE binds to adrenergic receptors, which principally include β1, β2, α1, and α2
- ACh action is terminated by metabolism in the synaptic cleft by acetylcholinesterase and in the plasma by pseudocholinesterase

**Antibiotic Allergies - What is the Risk of Cross-Reactivity?**

- In clinical practice, cross-reactivity between drugs presents a problem for both patients and physicians
- In the case of penicillin allergy, cross-reactivity to cephalosporins is less than 2%, however, in patients who have a history of true anaphylactic reaction, cross-reactivity is closer to 40%
- Conversely, cross-reactivity between penicillins and carbapenems is <1%
- The term "sulfa allergy" is often misused and has no formal definition. Current evidence suggests cross-reactivity between sulfonamide antibiotics (e.g. sulfamethoxazole-trimethoprim) and non-antibiotic sulfonamides, including loop diuretics (e.g. furosemide), thiazide diuretics (e.g. hydrochlorothiazide), protease inhibitors containing an arylamine group (e.g. darunavir), carbonic anhydrase inhibitors (e.g. acetazolamide), and sulfonylureas (e.g. glipizide)

**Examples of Clinically Relevant Drug Interactions**

| Interaction | Potential Effect | Mechanism of Interaction |
|---|---|---|
| Warfarin plus ciprofloxacin, clarithromycin, erythromycin, metronidazole, or trimethoprim-sulfamethoxazole | Increased effect of warfarin | Uncertain (Likely PD – antibiotic interference with enteric flora mediated Vitamin K2 production) |
| Warfarin plus acetaminophen | Acetaminophen (NAPQI) further increases INR | PD (reduction of Vitamin K-dependent clotting factors by NAPQI) |
| **Oral contraceptive pills** plus rifampin | Decreased effectiveness of oral contraception | PD and PK (rifamycin induced increase in hormone metabolism and Cyp3A4 induction) |
| **Sildenafil** plus nitrates | Hypotension | PD (PDE5 inhibitors potentiate cGMP production, nitrates increased production) |
| **SSRI** plus St. John's wort, naratriptan, rizatriptan, sumatriptan, zolmitriptan | Serotonin syndrome | PD (concomitant use of seretonergic medications) |
| SSRI plus selegiline or non-selective MAO-I | Serotonin syndrome | PD (decrease metabolism of sereteonin with excess serotonin in synaptic clef) |
| Some **HMG-CoA reductase inhibitors** plus niacin, gemfibrozil, erythromycin or itraconazole | Possible rhabdomyolysis | PK (various mechanisms based on drugs listed; Cyp3A or OATP1B1) |
| Sulfamethoxazole-Trimethoprim and ACEIs/ARBs, spironolactone | Increased risk of hyperkalemia | PD (reduced renal potassium excretion due to trimethoprim) |

- acetylcholinesterase inhibitors (pyridostigmine, donepezil, galantamine, rivastigmine) can be used to increase ACh levels in conditions such as myasthenia gravis or Alzheimer's disease
- NE action is terminated by reuptake at the presynaptic membrane, diffusion from the synaptic cleft, and degradation at monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT)

# Parasympathetic Nervous System

- blood vessels, adrenals, sweat glands, spleen capsule, and adrenal medulla do NOT have parasympathetic innervation
- parasympathetic pre-ganglionic fibres originate in the lower brainstem from cranial nerves III, VII, IX, X, and in the sacral spinal cord at levels S2-S4 and connect with post-ganglionic fibres via nicotinic receptors in ganglionic cells located near or within the target organ
- post-ganglionic fibres connect with effector tissues via:
  - M1 muscarinic receptors located in the CNS
  - M2 muscarinic receptors located in smooth muscle, cardiac muscle, and glandular epithelium

# Sympathetic Nervous System

- sympathetic pre-ganglionic fibres originate in the spinal cord at spinal levels T1-L2/L3
- pre-ganglionic fibres connect with post-ganglionic fibres via nicotinic receptors located in one of two groups of ganglia:
  1. paravertebral ganglia (i.e. the sympathetic trunk) that lie in a chain close to the vertebral column
  2. pre-vertebral ganglia (i.e. celiac and mesenteric ganglia) that lie within the abdomen
- post-ganglionic fibres connect with effector tissues via:
  - β1 receptors in cardiac tissue
  - β2 receptors in smooth muscle of bronchi and GI tract
  - α1 receptors in vascular smooth muscle
  - α2 receptors in vascular smooth muscle
  - M3 muscarinic receptors located in sweat glands

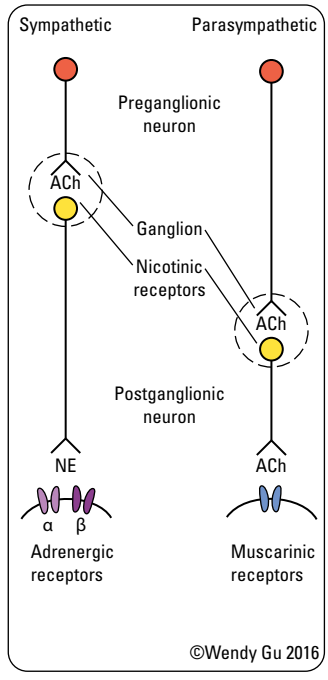



**Figure 8. Autonomic nervous system efferent tracts**

**Table 3. Direct Effects of Autonomic Innervation on the Cardiorespiratory System**

| Organ | Sympathetic NS | | Parasympathetic NS | |
|---|---|---|---|---|
| | Receptor | Action | Receptor | Action |
| **Heart** | | | | |
| 1. Sinoatrial | β1 | Increased HR | M | Decreased conduction |
| 2. Atrioventricular node | β1 | Increased conduction | M | Decreased conduction |
| 3. Atria | β1 | Increased contractility | M | Decreased conduction |
| 4. Ventricles | β1 | Increased contractility | M | Decreased HR |
| **Blood Vessels** | | | | |
| 1. Skin, splanchnic | α1, β2 | Constriction | M | Dilatation |
| 2. Skeletal muscle | α | Constriction | M | Dilatation |
| 3. Coronary | β2 (large muscles) | Dilatation | M | Dilatation |
| | α1, β2 | Constriction | M | Dilatation |
| | β2 | Dilatation | M | Dilatation |
| **Lungs** | | | | |
| 1. Bronchiolar smooth muscle | β2 | Relaxation | M | Constriction |
| 2. Bronchiolar glands | α1, β2 | Increased secretion | M | Stimulation |

# Opioid Therapy and Chronic Non-Cancer Pain

## General Management Principles

- when first considering therapy for patients with chronic non-cancer pain, optimize non-opioid pharmacotherapy and non-pharmacologic therapy, rather than a trial of opioids (strong recommendation)
- general approaches to opioid use should include avoiding initial high doses when possible and a slow, collaborative approach when tapering
- for patients with chronic non-cancer pain beginning opioid therapy, restrict the prescribed dose to less than 90 mg morphine equivalents daily (MED), and ideally less than 50 MED, rather than having no upper limit or a higher limit on dosing
  - for patients with chronic non-cancer pain who are currently using 90 mg morphine equivalents of opioids per day or more, encourage slow, collaborative taper opioids to the lowest effective dose, potentially including discontinuation, rather than making no change in opioid therapy
- for patients with chronic non-cancer pain who are using opioids and experiencing serious challenges in tapering, formal multidisciplinary program is suggested

- for more information, please refer to national opioid guidelines for a comprehensive approach to opioid use (link http://nationalpaincentre.mcmaster.ca/guidelines.html)

# Common Drug Endings

**Table 4. Common Drug Endings**

| Ending | Category | Example |
|---|---|---|
| -afil | PDE-5 inhibitor | sildenafil |
| -ane | Inhaled general anesthetic | halothane |
| -azepam | Benzodiazepine | lorazepam |
| -azole | Antifungal | ketoconazole |
| -caine | Local anesthetic | lidocaine |
| -mab | Monoclonal antibody | adalimumab |
| -nib | Small molecular inhibitors | imatinib |
| -olol | β-blocker | propranolol |
| -prazole | Proton pump inhibitor | omeprazole |
| -pril | ACE inhibitor | captopril |
| -sartan | ARB | candesartan |
| -statin | HMG-CoA inhibitor | atorvastatin |
| -terol | β2 agonist | albuterol |
| -tidine | H2 antagonist | cimetidine |
| -tropin | Pituitary hormone | somatotropin |
| -vir | Antiviral | acyclovir |
| -zosin | α1 antagonist | prazosin |

Note: Some medications are exceptions to the rule, e.g. methimazole (antithyroid)

For more information on medical pharmacology, please refer to our textbook product, Pharmacology You See

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# D Dermatology

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# Acronyms

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| β-hCG | β-human chorionic gonadotropin | DM | diabetes mellitus | MMR | measles/mumps/rubella | SSRI | selective serotonin reuptake inhibitor |
| AAFP | American Academy of Family Physicians | DRESS | drug reaction with eosinophilia and systemic symptoms | MRSA | methicillin-resistant *Staphylococcus aureus* | SSSS | staphylococcal scalded skin syndrome |
| ACEI | acetylcholinesterase inhibitor | DVT | deep vein thrombosis | MTP | metatarsal phalangeal | STI | sexually transmitted infection |
| AGEP | acute generalized exanthematous pustulosis | EM | erythema multiforme | NB-UVB | narrow band ultraviolet wavelength | TB | tuberculosis |
| AD | atopic dermatitis | ESR | erythrocyte sedimentation rate | Nd:YAG | neodymium-doped yttrium aluminum garnet | TEN | toxic epidermal necrolysis |
| AK | actinic keratosis | Fe | iron | NMN | nevomelanocytic nevus | TMP/SMX | trimethoprim-sulfamethoxazole |
| ASO | anti-streptolysin O | FTA-ABS | fluorescent treponemal antibody-absorption | NMSC | nonmelanoma skin cancers | TSH | thyroid stimulating hormone |
| BCC | basal cell carcinoma | GAS | group A β-hemolytic *Streptococcus* | NSAID | nonsteroidal anti-inflammatory drug | UC | ulcerative colitis |
| BCG | Bacillus Calmette-Guerin chemotherapy | GVHD | graft-versus-host disease | OCP | oral contraceptive pill | URTI | upper respiratory tract infection |
| BSA | body surface area | HHV | human herpes virus | OTC | over-the-counter | UV | ultraviolet |
| BUN | blood urea nitrogen | HPA | hypothalamic-pituitary-adrenal | PABA | para-aminobenzoic acid | UVA | ultraviolet A |
| CBC | complete blood count | HPV | human papillomavirus | PASI | psoriasis area and severity index | UVB | ultraviolet B |
| CMV | cytomegalovirus | HRT | hormone replacement therapy | PPD | purified protein derivative | UVC | ultraviolet C |
| CNS | central nervous system | HSV | herpes simplex virus | PUVA | psoralens and UVA | UVR | ultraviolet radiation |
| Cr | creatinine | HZV | herpes zoster virus | RA | rheumatoid arthritis | VDRL | venereal disease research laboratory |
| CXR | chest x-ray | IFN | interferon | SCC | squamous cell carcinoma | | |
| DIHS | drug induced hypersensitivity syndrome | IVIg | intravenous immunoglobulin | SHBG | sex hormone-binding globulin | VZV | varicella zoster virus |
| DLE | discoid lupus erythematosus | LFT | liver function test | SJS | Stevens-Johnson syndrome | | |
| | | MAOI | monoamine oxidase inhibitor | SLE | systemic lupus erythematosus | | |
| | | MM | malignant melanoma | SPF | sun protection factor | | |

# Introduction to Skin

## Skin Anatomy

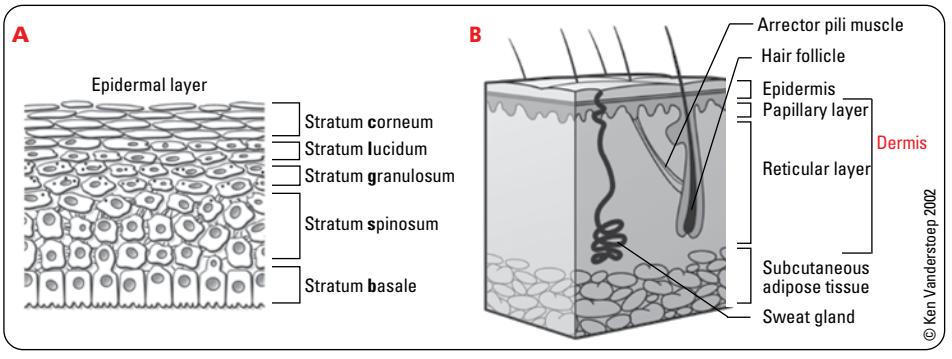



**Figure 1. Histologic layers of the skin. Epidermal layer is detailed in A**

**Layers of the Epidermis**
"**C**alifornians **L**ike **G**etting **S**un **B**urns"
OR
"**C**anadians **L**ike **G**ood **S**ushi **B**oxes"

### Skin

- divided anatomically into epidermis, dermis, and subcutaneous tissue
- **epidermis**
  - avascular: receives its nutrition from the dermal capillaries
  - derived from keratinocytes with the youngest presenting at the stratum basale
  - cells progress from stratum basale to stratum corneum in about 4 wk
    - stratum basale (germinativum): mitotic figures that give rise to keratinocytes
    - stratum spinosum (prickle cells): junctions in this layer (tonofilaments) give the epidermis its strength
    - stratum granulosum: flat cells containing basophilic granules
    - stratum lucidum: transparent layers of packed dead cells
    - stratum corneum: flat scales of the water-resistant protein keratin
  - cells of the epidermis
    - keratinocytes: located in all layers of the epidermis except the stratum corneum; connected to each other by desmosomes
    - melanocytes: located in the stratum basale; keratinocyte to melanocyte ratio in the basal layer is 10:1; melanocyte number is equal among races; produce melanosomes containing melanin, which are transferred to keratinocytes
    - Langerhans cells: dendritic cells which are important for immune surveillance
    - Merkel cells: located in the basal layer; involved in touch sensation
- **dermis**: comprised of connective tissue divided into two regions
  - papillary: contains numerous capillaries that supply nutrients to the dermis and epidermis
  - reticular: provides a strong structure for skin; consists of collagen bundles woven together along with elastic fibres, fibroblasts, and macrophages
  - cells of dermis
    - fibroblasts: produce collagen, elastin, and ground substance
    - mast cells: release histamines which mediate type I hypersensitivity
  - other components of dermis include: blood vessels, nerves, pilosebaceous units, and sweat glands
- **subcutaneous tissue** (hypodermis)
  - consists primarily of adipose cells, larger calibre vessels, nerves, and fascia

### Epidermal Appendages
- epidermal in origin, can extend into the dermis; includes hair, nails, and cutaneous glands
- pilosebaceous unit = hair + hair follicle + sebaceous gland + arrector pili muscle

### Cutaneous Glands
- **sebaceous gland**: part of pilosebaceous unit; produces sebum which is secreted into the hair follicle via the sebaceous duct, where it covers the skin surface (protective function)
  - sebum has some antifungal properties
  - these glands cover entire skin surface and are absent only in non-hair bearing areas (e.g. palms, soles, lips)
- **apocrine sweat gland**: apocrine duct empties into hair follicle above sebaceous gland
  - found in axillae and perineum
  - likely a vestigial structure, functions in other species to produce scent (e.g. pheromones)
- **eccrine sweat gland**: not part of pilosebaceous unit
  - found over entire skin surface except lips, nail beds, and glans penis
  - important in temperature regulation via secretion of sweat to cool skin surface

## Skin Function

- **protection**
  - due to continuous recycling and avascularity of epidermis
  - barrier to UV radiation (melanin), mechanical/chemical insults (sensory/mechanoreceptors), pathogens (immune cells), and dehydration (lipid rich barrier)
- **thermal regulation**
  - insulation to maintain body temperature in cool environments via peripheral vasoconstriction, hair, and subcutaneous adipose tissue
  - dissipation of heat in warm environments via increased activity of sweat glands and increased blood flow within dermal vascular networks
- **sensation**
  - touch, pain, and temperature sensation
- **metabolic function**
  - vitamin D synthesis
  - energy storage (mainly in the form of triglycerides)

# Morphology

## Primary Lesions

### Definition
- a de-novo initial lesion that has not been altered by trauma or manipulation, and has not regressed

**Table 1. Types of Primary Morphological Lesions**

| Profile | <1 cm Diameter | ≥1 cm Diameter |
|---|---|---|
| **Flat Lesion** | Macule (e.g. freckle) | Patch (e.g. vitiligo) |
| **Raised Superficial Lesion** | Papule (e.g. wart) | Plaque (e.g. psoriasis) |
| **Deep Palpable (dermal or subcutaneous) lesion** | Nodule (e.g. dermatofibroma) | Tumour (e.g. lipoma) |
| **Elevated Fluid-Filled Lesion** | Vesicle (e.g. HSV) | Bulla (e.g. bullous pemphigoid) |



**Describe a Lesion with SCALDA**

**S**ize and **S**urface area
**C**olour (e.g. hyperpigmented, hypopigmented, erythematous)
**A**rrangement (e.g. solitary, linear, reticulated, grouped, herpetiform)
**L**esion morphology
**D**istribution (e.g. dermatomal, intertriginous, symmetrical/asymmetrical, follicular)
**A**lways check hair, nails, mucous membranes and intertriginous areas

## Secondary Lesions

### Definition
- develop during the evolutionary process of skin disease, or created by manipulation, or due to complication of primary lesion (e.g. rubbing, scratching, infection)
- **crust**: dried fluid (serum, blood, or purulent exudate) originating from a lesion (e.g. impetigo)
- **scale**: excess keratin (e.g. seborrheic dermatitis)
- **lichenification**: thickening of the skin and accentuation of normal skin markings (e.g. chronic atopic dermatitis)
- **fissure**: a linear slit-like cleavage of the skin
- **excoriation**: a scratch mark
- **erosion**: a disruption of the skin involving the epidermis alone; heals without scarring
- **ulcer**: a disruption of the skin that extends into the dermis or deeper; may heal with scarring
- **xerosis**: pathologic dryness of skin (xeroderma), conjunctiva (xerophthalmia), or mucous membranes (xerostomia)
- **atrophy**: histological decrease in size or number of cells or tissues, resulting in thinning or depression of the skin

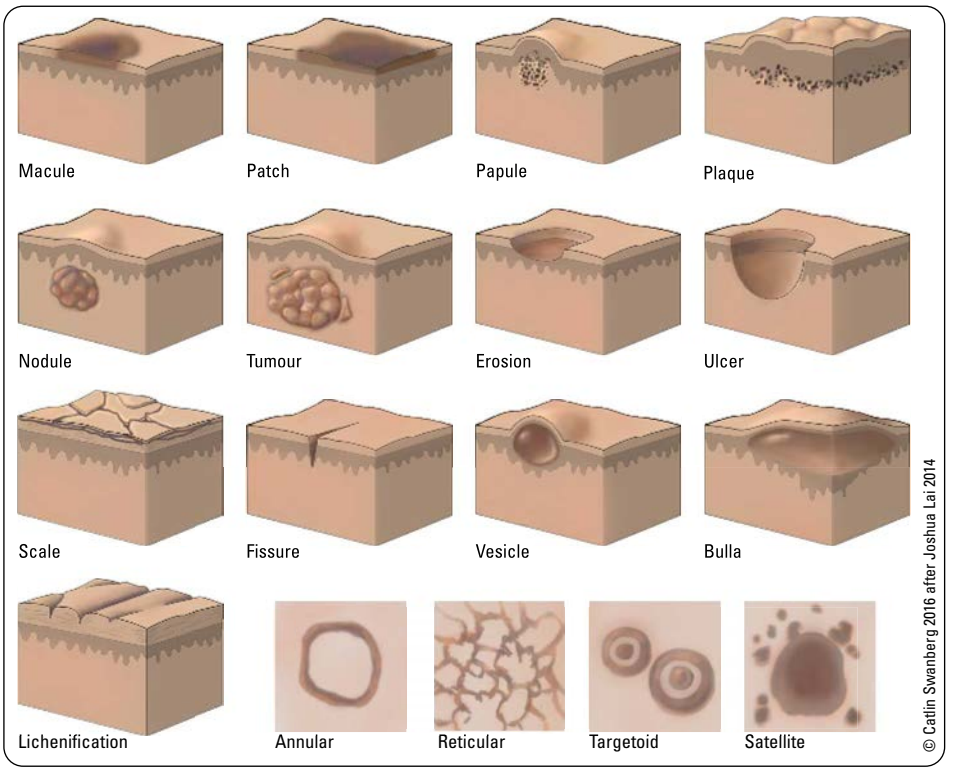



**Figure 2. Examples of primary and secondary morphology**

# Other Morphological Terms

- **cyst**: an internally epithelial-lined structure containing semi-solid material or fluid
- **pustule**: an elevated lesion containing a collection of neutrophils (infectious or inflammatory in nature)
- **scar**: replacement fibrosis of dermis and subcutaneous tissue (hypertrophic or atrophic)
- **wheal**: a special form of papule or plaque that is transient (<24 h) and blanchable, often with a halo and central clearing, formed by edema in the dermis (e.g. urticaria)
- **comedone**: a special collection of sebum and keratin
  - open comedo (blackhead)
  - closed comedo (whitehead)
- **petechiae**: pinpoint extravasation of blood into dermis resulting in hemorrhagic lesions; non-blanchable, <3 mm in size
- **purpura**: larger than petechia, 3 mm-1 cm in size
- **ecchymosis**: larger than purpura, >1 cm in size (i.e. a "bruise")
- **telangiectasia**: dilated superficial blood vessels; blanchable, reticulated, and of small calibre, can be associated with benign or malignant entities

# Patterns and Distribution

- **acral**: relating to the hands and feet (e.g. perniosis, secondary syphilis)
- **annular**: ring-shaped (e.g. granuloma annulare)
- **follicular**: involving hair follicles (e.g. folliculitis)
- **guttate**: lesions following a "drop-like" pattern (e.g. guttate psoriasis)
- **Koebner phenomenon**: i.e. isomorphic response, appearance of lesions at an injury site (e.g. lichen planus, psoriasis, vitiligo)
- **morbilliform**: literally means "measles-like", an eruption composed of macules and papules with truncal predominance
- **reticular**: lesions following a net-like pattern (e.g. livedo reticularis)
- **satellite**: small lesions scattered around the periphery of a larger lesion (e.g. candida diaper dermatitis)
- **serpiginous**: lesions following a snake-like pattern (e.g. cutaneous larva migrans)
- **target/targetoid**: concentric ring lesions, like a dartboard (e.g. EM)
- **other descriptive terms**: discrete, clustered, linear, confluent, dermatitic, indurated (i.e. hard or firm)

# Differential Diagnoses of Common Presentations

**Table 2. Differential Diagnosis of Common Presenting Problems**

| Lesion | Infectious | Inflammatory | Drug/Toxin | Miscellaneous |
|---|---|---|---|---|
| **Brown Macule** | | Post-inflammatory hyperpigmentation | UV radiation, actinic/solar lentigo, freckle (ephelide) | Congenital: café-au-lait spots, congenital nevus, epidermal/junctional nevus<br>Neoplasia: lentigo maligna, MM, pigmented BCC<br>Other: melasma/chloasma ("mask of pregnancy") |
| **Discrete Red Papule** | Folliculitis<br>Furuncle<br>Scabies | Acne vulgaris<br>Rosacea<br>Psoriasis<br>Urticaria | Bites/stings | Autoimmune: lichen planus; see *Papulosquamous Diseases*, D16<br>Vascular: hemangioma, pyogenic granuloma<br>Other: dermatofibroma, miliaria rubra |
| **Red Scales** | Pityriasis rosea<br>Secondary syphilis<br>Tinea | Dermatitis (atopic, contact, nummular, seborrheic)<br>Discoid lupus<br>Psoriasis | Gold | Autoimmune: lichen planus; see *Papulosquamous Diseases*, D16<br>Neoplastic: mycosis fungoides |
| **Vesicle** | Cat scratch disease<br>Impetigo<br>Viral: HSV, HZV, VZV, Molluscum, Coxsackie, Scabies | Acute contact dermatitis<br>Dyshidrotic eczema | | Other: dermatitis herpetiformis, porphyria cutanea tarda |
| **Bulla** | Bullous impetigo | Acute dermatitis<br>EM, SLE, SJS/TEN | Fixed drug eruption<br>SJS/TEN | Autoimmune: bullous pemphigoid, pemphigus vulgaris<br>Other: dermatitis herpetiformis, porphyria cutanea tarda |
| **Pustule** | Candida<br>Dermatophyte<br>Impetigo<br>Sepsis<br>Varicella | Acne vulgaris<br>Rosacea<br>Dyshidrotic dermatitis<br>Pustular folliculitis<br>Pustular psoriasis<br>Hidradenitis suppurativa | Acute generalized exanthematous pustulosis (usually secondary to drug reaction) | |
| **Oral Ulcer** | Aspergillosis<br>CMV<br>Coxsackie<br>Cryptococcosis<br>HSV/HZV<br>HIV, TB, Syphilis | Allergic stomatitis<br>EM<br>Lichen planus<br>Seronegative arthropathies, SLE<br>Recurrent aphthous stomatitis<br>Behçet's disease | Chemotherapy<br>Radiation therapy<br>SJS/TEN | Autoimmune: pemphigus vulgaris<br>Congenital: XXY<br>Hematologic: sickle cell disease<br>Neoplasia: BCC, SCC |
| **Skin Ulcer** | Plague<br>Syphilis<br>TB<br>Tularemia | RA, SLE, vasculitis<br>UC (pyoderma gangrenosum) | | Autoimmune: necrobiosis lipoidica diabeticorum (e.g. DM)<br>Congenital: XXY<br>Hematologic: sickle cell disease<br>Neoplasia: SCC<br>Vascular: arterial, neurotrophic, pressure, venous, aphthous, leukoplakia, traumatic |

# Common Skin Lesions

## Cysts

**Table 3. Cysts**

| | Clinical Feature | Pathophysiology | Epidemiology | Clinical Course | Management |
|---|---|---|---|---|---|
| **Epidermal Cyst** | Round, yellow/flesh-coloured, slow growing, mobile, firm, fluctuant, nodule or tumour | Epithelial cells displaced into dermis, epidermal lining becomes filled with keratin and lipid-rich debris<br>May be post-traumatic, rarely syndromic | Most common cutaneous cyst in youth – middle age | Central punctum may rupture (foul, cheesy odour, creamy colour) and produce inflammatory reaction<br>Can increase in size and number over time | No treatment<br>Elective excision |
| **Pilar Cyst** (Trichilemmal) | Multiple, hard, variable sized nodules under the scalp, lacks central punctum | Thick-walled cyst lined with stratified squamous epithelium and filled with dense keratin<br>Idiopathic<br>Post-trauma | 2nd most common cutaneous cyst<br>F>M, hereditary | Rupture causes pain and inflammation | No treatment<br>Elective excision |
| **Dermoid Cyst** | Firm nodule most commonly found at lateral third of eyebrow or midline under nose | Rare, congenital hamartomas, which arise from inclusion of epidermis along embryonal cleft closure lines, creating a thick-walled cyst filled with dense keratin | Rare | If nasal midline, risk of extension into CNS | No treatment<br>Elective excision |
| **Ganglion Cyst** | Usually solitary, rubbery, translucent; a clear gelatinous viscous fluid may be extruded | Cystic lesion that originates from joint or tendon sheath, called a digital mucous cyst when found on fingertip<br>Associated with osteoarthritis | Older age | Stable | No treatment<br>Incision and expression of contents<br>Elective excision |
| **Milium** | 1-2 mm superficial, white to yellow subepidermal papules occurring on eyelids, cheeks, and forehead | Small epidermoid cyst, primarily arising from pluripotential cells in epidermal or adnexal epithelium<br>Can be secondary to blistering, ulceration, trauma, topical corticosteroid atrophy, or cosmetic procedures | Any age<br>40-50% of infants | In newborns, spontaneously resolves in first 4 wk of life | No treatment<br>Incision and expression of contents<br>Electrodessication<br>Topical retinoid therapy |

# Fibrous Lesions

## DERMATOFIBROMA

### Clinical Feature
- button-like, firm dermal papule or nodule, skin-coloured to red-brown
- majority are asymptomatic but may be pruritic and/or tender
- site: legs > arms > trunk
- dimple sign (Fitzpatrick's sign): lateral compression causes dimpling of the lesion

### Pathophysiology
- benign tumour due to fibroblast proliferation in the dermis

### Etiology
- unknown; may be associated with history of minor trauma (e.g. shaving or insect bites)
- eruptive dermatofibroma can be associated with SLE

### Epidemiology
- adults, F>M

### Differential Diagnosis
- dermatofibrosarcoma protuberans, malignant melanoma, Kaposi's sarcoma, blue nevus

### Investigations
- biopsy if diagnosis is uncertain

### Management
- no treatment required
- excision if bothersome

## SKIN TAGS

### Clinical Feature
- small (1-10 mm), soft, skin-coloured or darker pedunculated papule, often polypoid
- sites: eyelids, neck, axillae, inframammary, and groin

**Skin tags are also known as…**
- Acrochordons
- Fibroepithelial polyps

### Pathophysiology
- benign outgrowth of skin

### Epidemiology
- middle-aged and elderly, F>M, obese, can increase in size and number during pregnancy

### Differential Diagnosis
- pedunculated seborrheic keratosis, compound or dermal melanocytic nevus, neurofibroma, fibroepithelioma of Pinkus (rare variant of BCC), nevus lipomatosis superficialis

### Management
- excision, electrodessication, cryosurgery

# Hyperkeratotic Lesions

## SEBORRHEIC KERATOSIS

### Clinical Feature
- known as 'wisdom spots,' 'age spots,' or 'barnacles of life'
- well-demarcated waxy papule/plaque with classic "stuck on" appearance
- rarely pruritic
- over time lesions appear more warty, greasy and pigmented
- sites: face, trunk, upper extremities (may occur at any site except palms or soles)

### Pathophysiology
- very common benign epithelial tumour due to proliferation of keratinocytes and melanocytes

### Epidemiology
- unusual <30 yr old
- M>F
- autosomal dominant inheritance
- Leser-Trelat: sudden appearance of SK that can be associated with malignancy, commonly gastric adenocarcinomas

### Differential Diagnosis
- malignant melanoma (lentigo maligna, nodular melanoma), melanocytic nevi, pigmented BCC, solar lentigo, spreading pigmented AK

### Investigations
- biopsy only if diagnosis uncertain

### Management
- none required, for cosmetic purposes only
- cryotherapy, electrodessication, excision

## ACTINIC KERATOSIS (SOLAR KERATOSIS)
- see *Pre-Malignant Skin Conditions*, D33

## KERATOACANTHOMA
- see *Malignant Skin Tumours*, D34

## CORNS (HELOMATA)

### Clinical Feature
- firm papule with a central, translucent, cone-shaped, hard keratin core
- painful with direct pressure
- sites: most commonly on dorsolateral fifth toe and dorsal aspects of other toes

### Pathophysiology
- localized hyperkeratosis induced by pressure on hands and feet

### Epidemiology
- F>M, can be caused by chronic microtrauma

### Differential Diagnosis
- calluses, plantar warts

### Management
- relieve pressure with padding or alternate footwear, orthotics
- paring, topical salicylic acid

**Corns vs. Warts vs. Calluses**
- Corns have a whitish yellow central translucent keratinous core; painful with direct pressure; interruption of dermatoglyphics
- Warts bleed with paring and have a black speckled central appearance due to thrombosed capillaries; plantar warts destroy dermatoglyphics (epidermal ridges)
- Calluses have layers of yellowish keratin revealed with paring; there are no thrombosed capillaries or interruption of epidermal ridges

# Keloids

### Clinical Feature
- firm, shiny, skin-coloured or red-bluish papules/nodules that most often arise from cutaneous injury (e.g. piercing, surgical scar, acne), but may appear spontaneously
- extends beyond the margins of the original injury, and may continue to expand in size for yr with claw-like extensions
- can be pruritic and painful
- sites: earlobes, shoulders, sternum, scapular area, angle of mandible

### Pathophysiology
- excessive deposition of randomly organized collagen fibres following trauma to skin

### Epidemiology
- most common in black patients, followed by those of Asian descent (predilection for darker skin)
- M=F, all age groups

### Management
- intralesional corticosteroid injections
- silicone compression

**Keloids vs. Hypertrophic Scars**
- **Keloids:** extend beyond margins of original injury with claw-like extensions
- **Hypertrophic scars:** confined to original margins of injury

# Pigmented Lesions

## CONGENITAL NEVOMELANOCYTIC NEVI (CNMN)

### Clinical Feature
- sharply demarcated pigmented papule or plaque with regular borders ± coarse hairs
- classified by size: small (<1.5 cm), medium (M1: 1.5-10 cm, M2: >10-20 cm), large (L1: >20-30 cm, L2 >30-40 cm), giant (G1: >40-60 cm, G2: >60 cm)
- may be surrounded by smaller satellite nevi

### Pathophysiology
- nevomelanocytes in epidermis (clusters) and dermis (strands)

### Epidemiology
- present at birth or develops in early infancy to childhood
- malignant transformation is rare (1-5%) and more correlated with size of the lesion
- neurocutaneous melanosis can occur in giant CNMN (melanocytes in the CNS)

### Management
- take a baseline photo and observe lesion for change in shape, colour, or size out of proportion of growth
- surgical excision if suspicious, due to increased risk of melanoma
- MRI if suspicious for neurological involvement

**DDx of Hyperpigmented Macules**
- Purpura (e.g. solar, ASA, anticoagulants, steroids, hemosiderin stain)
- Post-inflammatory
- Melasma
- Melanoma
- Fixed drug eruption

## OTHER CONGENITAL PIGMENTED LESIONS

**Table 4. Comparison of Other Congenital Pigmented Lesions**

| | Clinical Feature | Pathophysiology | Epidemiology | Differential Diagnosis | Clinical Course and Management |
|---|---|---|---|---|---|
| **Café-au-lait Macule** | Flat light brown lesions with smooth or jagged borders | Areas of increased melanogenesis | 6 or more is suggestive of neurofibromatosis type I<br>Also associated with McCune-Albright syndrome | Flat congenital melanocytic nevus, speckled lentiginous nevus | Enlarge in proportion to the child<br>No effective treatment |
| **Speckled Lentiginous Nevus** (nevus spilus) | Brown pigmented macular background (café-au-lait macule-like) with dark macular or papular speckles | Increased melanocyte concentration | Risk of melanoma similar to that of a CNMN of the same size | Café-au-lait macule, agminated lentigines, Becker's nevus | Usually the light macular background is present at birth and speckles develop over time<br>Management is similar to that of CNMNs |
| **Dermal Melanocytosis** (historically known as Mongolian Spot) | Congenital grey-blue solitary or grouped macules commonly on lumbosacral area | Ectopic melanocytes in dermis | 99% occurs in Asian and Indigenous infants | Ecchymosis | Usually fades in early childhood but may persist into adulthood |

**Other Nevi**
- **Halo nevus**: often a typical appearing nevus surrounded by a ring of depigmentation; not rare in children; uncommonly associated with vitiligo; no treatment required unless irregular colour or borders
- **Blue nevus**: round to oval macule/papule with homogenous blue to blue-black colour; often appears in childhood and late adolescence; no treatment required unless atypical features are noted

## ACQUIRED NEVOMELANOCYTIC NEVI

### Clinical Feature
- common mole: well circumscribed, round, uniformly pigmented macules/papules <1.5 cm
- average number of moles per person: 18-40
- 3 stages of evolution: junctional NMN, compound NMN, and dermal NMN

**Table 5. Evolution of Acquired Nevomelanocytic Nevi**

| Type | Age of Onset | Clinical Feature | Histology |
|---|---|---|---|
| **Junctional** | Childhood<br>Majority progress to compound nevus | Flat, regularly bordered, uniformly tan-dark brown, sharply demarcated macule | Melanocytes at dermal-epidermal junction above basement membrane |
| **Compound** | Any age | Domed, regularly bordered, smooth, round, tan-dark brown papule<br>Face, trunk, extremities, scalp<br>NOT found on palms or soles | Melanocytes at dermal-epidermal junction; migration into dermis |
| **Dermal** | Adults | Soft, dome-shaped, skin-coloured to tan/brown papules or nodules<br>Sites: face, neck | Melanocytes exclusively in dermis |

### Management
- new or changing pigmented lesions should be evaluated for atypical features which could indicate a melanoma
- excisional biopsy should be considered if the lesion demonstrates rapid change, asymmetry, varied colours, irregular borders and persistent pruritus or bleeding

## OTHER ACQUIRED PIGMENTED LESIONS

**Table 6. Comparison of Other Acquired Pigmented Lesions**

| | Clinical Feature | Pathophysiology | Epidemiology | Differential Diagnosis | Clinical Course and Management |
|---|---|---|---|---|---|
| **Atypical Nevus** (Dysplastic Nevus) | Variegated macule/papule with irregular distinct melanocytes in the basal layer<br>Risk factors: family history | Hyperplasia and proliferation of melanocytes extending beyond dermal compartment of the nevus<br>Often with region of adjacent nests | >5 atypical nevi increase risk for melanoma<br>Numerous dysplastic nevi may be part of familial atypical mole and melanoma syndrome | Melanoma | Follow with baseline photographs for changes<br>Excisional biopsy if lesion changing or highly atypical<br>Close surveillance with whole body skin examination |
| **Ephelides** (Freckles) | Small (<5 mm) well-demarcated light brown macules<br>Sites: sun-exposed skin | Increased melanin within basal layer keratinocytes secondary to sun exposure | Skin phototypes I-II most commonly | Junctional nevi<br>Juvenile lentigines | Multiply and darken with sun exposure, fade in winter<br>No treatment required<br>Sunscreen and sun avoidance may prevent the appearance of new freckles |
| **Solar Lentigo** (Liver Spot) | Well-demarcated brown/black macules<br>Sites: sun-exposed skin | Benign melanocytic proliferation in dermal-epidermal junction due to chronic sun exposure | Most common in Caucasians >40 yr<br>Skin phototypes I-III most commonly | Lentigo maligna, seborrheic keratosis, pigmented actinic keratosis | Laser therapy, shave excisions, cryotherapy |
| **Becker's Nevus** | Hairy, light brown macule/patch with a papular verrucous surface<br>Sites: trunk and shoulders, onset in teen yr | Pigmented hamartoma with increased melanin in basal cells | M>F<br>Often becomes noticeable at puberty | Hairy congenital melanocytic nevus | Hair growth follows onset of pigmentation<br>Cosmetic management (usually too large to remove) |
| **Melasma** | Symmetrical hyperpigmentation on sun-exposed areas of face (forehead, upper lip, cheeks, chin) | Increase in number and activity of melanocytes<br>Associated with estrogen and progesterone | F>M<br>Common in pregnancy and women taking OCP or HRT<br>Risk factors: sun exposure, dark skin tone<br>Can occur with mild endocrine disturbances, antiepileptic medications and other photosensitizing drugs | Post-inflammatory hyperpigmentation | Often fades over several mo after stopping hormone treatment or delivering baby<br>Treatment: hydroquinone, azelaic acid, retinoic acid, topical steroid, combination creams, destructive modalities (chemical peels, laser treatment), camouflage make-up, sunscreen, sun avoidance |

# Vascular Lesions

**Table 7. Vascular Tumours Compared to Vascular Malformations**

| | Vascular Tumours | Vascular Malformations |
|---|---|---|
| **Definition** | Endothelial hyperplasia | Congenital malformation with normal endothelial turnover |
| **Presence at Birth** | Usually postnatal | 100% at birth (not always obvious) |
| **M:F** | 1:3-5 | 1:1 |
| **Natural History** | Phases<br>Proliferating<br>Involuting<br>Involuted | Proportionate growth (can expand) |

## HEMANGIOMAS

### Clinical Feature
- red or blue subcutaneous mass that is soft/compressible, blanches with pressure; feels like a "bag of worms" when palpated

A spider angioma will blanch when the tip of a paperclip is applied to the centre of the lesion

### Pathophysiology
- benign vascular tumour
- includes: cavernous hemangioma, capillary/infantile hemangioma, spider hemangioma

**Table 8. Vascular Tumours**

| | Clinical Feature | Pathophysiology | Epidemiology | Clinical Course | Management |
|---|---|---|---|---|---|
| **Hemangioma of Infancy** | Hot, firm red to blue plaques or tumours | Benign vascular proliferation of endothelial lining | Appears shortly after birth; rarely may be congenital | Appears shortly after birth, increases in size over months, then regresses<br>50% of lesions resolve spontaneously by 5 yr | 10% require treatment due to functional impairment (visual compromise, airway obstruction, high output cardiac failure) or cosmesis<br>Consider treatment if not gone by school age; topical timolol, propranolol; systemic corticosteroids; laser treatment; surgery<br>Provide early specialist referral or treatment in infants with high-risk hemangiomas |
| **Spider Angioma (Campbell Telangiectasia)** | Central red arteriole with slender branches, blanchable | Can be associated with hyperestrogenic state (e.g. in liver disease, pregnancy, OCP) but more often is not | Any age | Increase in number over time | Reassurance<br>Electrodesiccation or laser surgery if patient wishes |
| **Cherry Angioma (Campbell De Morgan Spot)** | Bright red to deep maroon, dome-shaped vascular papules, 1-5 mm<br>Site: trunk<br>Less friable compared to pyogenic granulomas | Benign vascular neoplasm | >30 yr old | Lesions do not fade in time<br>Lesions bleed infrequently | Usually no treatment needed<br>Laser or electrocautery for small lesions<br>Excision of large lesions if necessary |
| **Pyogenic Granuloma** | Bright red, dome-shaped sessile or pedunculated friable nodule<br>Sites: fingers, lips, mouth, trunk, toes<br>DDx: glomus tumour, nodular MM, SCC, nodular BCC | Rapidly developing hemangioma<br>Proliferation of capillaries with erosion of epidermis and neutrophilia | <30 yr old | Lesion grows rapidly over wk-mo, then stabilizes<br>Lesion may persist indefinitely if untreated | Surgical excision with histologic examination<br>Electrocautery; laser; cryotherapy |

## VASCULAR MALFORMATIONS

**Table 9. Vascular Malformations**

| Type | Clinical Feature | Pathophysiology | Management |
|---|---|---|---|
| **Nevus Flammeus** (Port-wine stain) | Red to blue macule present at birth that follows a dermatomal distribution, rarely crosses midline<br>Most common site: nape of neck<br>Never spontaneously regresses but grows in proportion to the child | Congenital vascular malformation of dermal capillaries; rarely associated with Sturge-Weber syndrome (V1, V2 distribution) | Laser or make-up |
| **Nevus Simplex** (salmon patch) | Pink-red irregular patches<br>Midline macule on glabella known as "Angel Kiss"; on nuchal region known as "Stork Bites"<br>Present in 1/3 of newborns<br>Majority regress spontaneously | Congenital dilation of dermal capillaries | No treatment required |



Pyogenic granuloma is a misnomer: it is neither pyogenic nor granulomatous



**Venous Lake:** benign blue or violaceous papular lesion occurring on the face, lips, and ears due to dilation of a venule. Distinguished from malignant pigmented lesions through diascopy, as compression blanches the lesion

# Lipoma

### Clinical Feature
- single or multiple non-tender subcutaneous tumours that are soft and mobile
- occurs most frequently on the trunk, and extremities but can be anywhere on the body

### Pathophysiology
- adipocytes enclosed in a fibrous capsule

### Epidemiology
- often solitary or few in number, if multiple can be associated with rare syndromes

### Differential Diagnosis
- angiolipoma, liposarcoma

### Investigations
- biopsy only if atypical features (painful, rapid growth, firm)

### Management
- reassurance
- excision or liposuction only if desired for cosmetic purposes

# Acneiform Eruptions

## Acne Vulgaris/Common Acne

### Clinical Feature
- a common inflammatory pilosebaceous disease categorized with respect to severity
  - Type I: comedonal, sparse, no scarring
  - Type II: comedonal, papular, moderate ± little scarring
  - Type III: comedonal, papular, and pustular, with scarring
  - Type IV: nodulocystic acne, risk of severe scarring
- sites of predilection: face, neck, upper chest, and back

### Pathophysiology
- hyperkeratinization at the follicular ostia (opening) blocks the secretion of sebum leading to the formation of microcomedones
- androgens promote excess sebum production
- *Cutibacterium* acnes metabolize sebum to free fatty acids and produces pro-inflammatory mediators

### Epidemiology
- age of onset in puberty (10-17 yr in females, 14-19 yr in males)
- in prepubertal children consider underlying hormonal abnormality (e.g. late onset congenital adrenal hyperplasia)
- incidence decreases in adulthood
- genetic predisposition: majority of individuals with cystic acne have parent(s) with history of severe acne

### Differential Diagnosis
- folliculitis, keratosis pilaris (upper arms, face, thighs), perioral dermatitis, rosacea

**Table 10. Management of Acne**

| Compound/Drug Class | Product Names | Notes |
|---|---|---|
| **MILD ACNE: Topical Therapies OTC** | | |
| **Benzoyl peroxide** (BPO) | Solugel®, Benzac®, Desquam®, Fostex® | Helps prevent *C. acnes* resistance, is a bactericidal agent (targets *P. acnes*) and is comedolytic |
| **Salicylic acid** | Akurza® Cream, DermalZone | Used when patients cannot tolerate a topical retinoid due to skin irritation |
| **MILD ACNE: Prescription Topical Therapies** | | |
| **Antimicrobials** | Clindamycin (Dalacin T), Erythromycin | High rate of resistance when used as monotherapy |
| **Retinoids** | Vitamin A Acid (Tretinoin, Stieva-A, Retin A), Adapalene (Differin) | Backbone of topical acne therapy<br>All regimens should include a retinoid unless patient cannot tolerate |
| **Combination products** | Clindoxyl (Clindamycin and BPO)<br>Benzaclin (Clindamycin and BPO)<br>TactuPump (Adapalene and BPO)<br>Biacna (Clindamycin and Tretinoin)<br>Benzamycine (BPO and Erythromycin) | Allows for greater adherence and efficacy<br>Combines different mechanisms of action to increase efficacy and maximize tolerability |
| **MODERATE ACNE** | | |
| **Tetracycline/Minocycline/ Doxycycline** | Sumycin/Minocin/Vibramycin | Use caution with regard to drug interactions: do not use with isotretinoin<br>Sun sensitivity<br>Antibiotics require 3 mo of use before assessing efficacy |
| **Cyproterone acetate-ethinyl estradiol** | Diane-35® | After 35 yr of age, estrogen/progesterone should only be considered in exceptional circumstances, carefully weighing the risk/benefit ratio with physician guidance |
| **Spironolactone** | Aldactone | May cause hyperkalemia if concurrent renal dx<br>Black box warning for breast cancer |
| **SEVERE ACNE** | | |
| **Isotretinoin** | Accutane®, Clarus®, Epuris® | See Table 27 for full side effect profile<br>Most adverse effects are temporary and will resolve when the drug is discontinued<br>Baseline lipid profile (risk of hypertriglyceridemia), LFTs and β-hCG before treatment<br>May transiently exacerbate acne before patient sees improvement<br>Refractory cases may require multiple courses of isotretinoin |

**Treatment of Acne Scars**
- Tretinoin creams
- Glycolic acid
- Chemical peels for superficial scars
- Injectable fillers (collagen, hyaluronic acid) for pitted scars
- Fraxel laser
- $CO_2$ laser resurfacing

**Acne Myths Debunked**
- Eating greasy food and chocolate does not cause or worsen acne
- Blackheads (comedones) are black because of oxidized fatty acids, not dirt
- Acne is not caused by poor hygiene; on the contrary, excessive washing of face can be an aggravator

Antibiotics are used in inflammatory skin conditions since they also have anti-inflammatory properties (e.g. macrolides in acne). Topical antibiotics may also be used to treat secondary bacterial superinfections (e.g. impetigo)

**Acne Exacerbating Factors**
- Systemic medications: lithium, phenytoin, steroids, halogens, androgens, iodides, bromides, danazol
- Topical agents: steroids, tars, ointments, oily cosmetics
- Mechanical pressure or occlusion, such as leaning face on hands
- Emotional stress

A combination of topical retinoids and topical erythromycin or clindamycin is more effective than either agent used alone

**Intralesional Injections**
Intralesional corticosteroid injections are effective in the treatment of individual acne nodules

**Isotretinoin and Pregnancy**
- Use of isotretinoin during pregnancy is associated with spontaneous abortion and major birth defects such as facial dysmorphism and cognitive impairment
- Pregnancy should be ruled out before starting isotretinoin
- Patients should use 2 forms of contraception while on isotretinoin

# Perioral Dermatitis

### Clinical Feature
- discrete erythematous micropapules that often become confluent, forming inflammatory plaques on perioral, perinasal, and periorbital skin
- commonly symmetrical, rim of sparing around vermillion border of lips

### Epidemiology
- 15-40 yr old, occasionally in younger children
- predominantly females

### Differential Diagnosis
- contact dermatitis, rosacea, acne vulgaris

### Management
- avoid all topical steroids
- topical: metronidazole 0.75% gel or 0.75-1% cream to affected area bid
- systemic: tetracycline family antibiotic (utilized for its anti-inflammatory properties)
- occasional use of a non-steroidal anti-inflammatory cream (i.e. tacrolimus or pimecrolimus)

**Important Controversies Associated with Isotretinoin Therapy for Acne**
Am J Clin Dermatol 2013;14:71-76
**Main Points**:
1. The evidence on whether isotretinoin causes depression and suicide is inconsistent; however, numerous controlled studies have shown an improvement in anxiety and depression scores in those taking isotretinoin.
2. There is no association between IBD and isotretinoin use. Only one study showed a significantly increased risk of UC. When considering using isotretinoin in a patient with IBD or with a strong family history, consider involving a gastroenterologist.

# Rosacea

### Clinical Feature
- dome-shaped inflammatory papules ± pustules
- flushing, non-transient erythema, and telangiectasia
- distribution: typically on central face including forehead, nose, cheeks, and chin; rarely on scalp, neck, and upper body
- characterized by remissions and exacerbations
- exacerbating factors: heat, cold, wind, sun, stress, drinking hot liquids, alcohol, spices
- all forms of rosacea can progress from mild to moderate to severe
- rarely in longstanding rosacea, signs of thickening, induration and lymphedema in the skin can develop
- phyma: a distinct swelling caused by lymphedema and hypertrophy of subcutaneous tissue, particularly affecting the nose (rhinophyma)
- ocular manifestations: blepharoconjunctivitis, keratitis, iritis

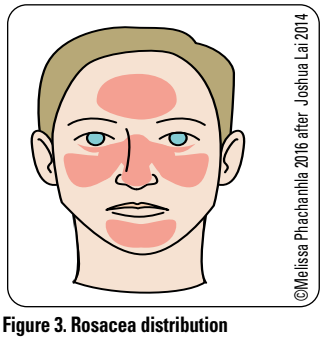


**Figure 3. Rosacea distribution**

### Pathophysiology
- unknown

### Epidemiology
- although found in all skin types, highest prevalence in fair-skinned people
- 30-50 yr old; F>M

### Differential Diagnosis
- acne vulgaris, seborrheic dermatitis, perioral dermatitis, contact dermatitis

### Management
- trigger avoidance and daily sunscreen use for long-term management
- avoid topical corticosteroids
- telangiectasia: treated by physical ablation; electrical hyfrecators, vascular lasers, and intense pulsed light therapies
- phymas: treated by physical ablation or removal; paring, electrosurgery, cryotherapy, laser therapy ($CO_2$, argon, Nd:YAG)

Rosacea can be differentiated from acne by the absence of comedones, a predilection for the central face and symptoms of flushing

**Guidelines for the Diagnosis of Rosacea**
J Drugs Dermatol 2012;11(6):725-730
Presence of one or more of the following primary features:
- Flushing (transient erythema)
- Nontransient erythema
- Papules and pustules
- Telangiectasia

May include one or more of the following secondary features:
- Burning or stinging
- Dry appearance
- Edema
- Phymatous changes
- Ocular manifestations
- Peripheral location

**Table 11. Specific Rosacea Treatments**

| 1st Line | 2nd Line | 3rd Line |
|---|---|---|
| Oral tetracyclines<br>Topical metronidazole<br>Oral erythromycin (250-500 mg PO bid)<br>Topical azelaic acid<br>Topical ivermectin | Topical clindamycin<br>Topical erythromycin 2% solution<br>Topical benzoyl peroxide<br>Oral metronidazole | Oral retinoids |

# Dermatitis (Eczema)

### Definition
- inflammation of the skin

### Clinical Feature
- poorly demarcated erythematous patches or plaques
- symptoms include pruritus and pain
- acute dermatitis: papules, vesicles
- subacute dermatitis: scaling, crusting, excoriations
- chronic dermatitis: lichenification, xerosis, fissuring

## Asteatotic Dermatitis

### Clinical Feature
- diffuse, mild pruritic dermatitis secondary to dry skin
- very common in elderly, especially in the winter (i.e. "winter itch") but starts in the fall
- shins predominate, looks like a "dried river bed"

### Management
- skin rehydration with moisturizing routine ± corticosteroid creams

## Atopic Dermatitis

### Clinical Feature
- subacute and chronic eczematous reaction associated with prolonged severe pruritus
- distribution depends on age
- inflammation, lichenification, excoriations are secondary to relentless scratching
- atopic palms: hyperlinearity of the palms (associated with ichthyosis vulgaris)
- associated with: keratosis pilaris (hyperkeratosis of hair follicles, "chicken skin"), xerosis, occupational hand dryness
- associated with severe or poorly controlled psychosocial distress and psychiatric comorbidities

### Epidemiology
- frequently affects infants, children, and young adults
- 10-20% of children in developed countries under the age of 5 are affected
- associated with personal or family history of atopy (asthma, hay fever), anaphylaxis, eosinophilia
- polygenic inheritance: one parent >60% chance for child; two parents >80% chance for child
- long-term condition with 1/3 of patients continuing to show signs of AD into adulthood

### Pathophysiology
- a T-cell driven inflammatory process with epidermal barrier dysfunction

### Investigations
- clinical diagnosis
- consider: skin biopsy, patch testing if allergic contact dermatitis is suspected

### Management
- goal: reduce signs and symptoms, prevent or reduce recurrences/flares
- better outcome (e.g. less flare-ups, modified course of disease) if diagnosis made early
- avoid triggers of AD
- be vigilant for depressive symptoms and the possible need for psychiatric referral, especially among those with severe disease
- non-pharmacologic therapy
  - moisturizers
  - apply liberally and reapply at least twice a day with goal of minimizing xerosis
  - include in treatment of mild to severe disease as well as in maintenance therapy
  - bathe in plain warm water for a short period of time once daily followed by lightly but not completely drying the skin with a towel; immediately apply topical agents or moisturizers after this
  - use fragrance-free hypoallergenic non-soap cleansers
- pharmacologic therapy
  - topical corticosteroids
    - effective in reducing acute and chronic symptoms as well as prevention of flares
    - choice of steroid potency depends on age, body site, short vs. long-term use
    - apply 1 adult fingertip unit (0.5 g) to an area the size of 2 adult palms bid for acute flares
    - local side effects: skin atrophy, purpura, telangiectasia, striae, hypertrichosis, and acneiform eruption are all very rarely seen

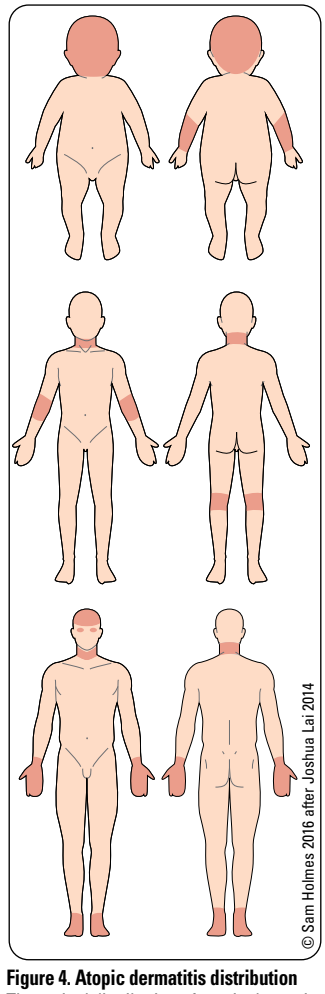



**Figure 4. Atopic dermatitis distribution**
The typical distribution of atopic dermatitis in infants <6 mo (top), children >18 mo (middle) and adults (bottom)

**Triggers for Atopic Dermatitis**
- Irritants (detergents, solvents, clothing, water hardness)
- Contact allergens
- Environmental aeroallergens (e.g. dust mites)
- Inappropriate bathing habits (e.g. long hot showers)
- Sweating
- Microbes (e.g. *S. aureus*)
- Stress

- topical calcineurin inhibitors
  - tacrolimus 0.03%, 0.1% (Protopic®) and pimecrolimus 1% (Elidel®)
  - use as steroid-sparing agents in the long-term
  - advantages over long-term corticosteroid use: sustained effect in controlling pruritus; no skin atrophy; safe for the face and neck
  - apply 2x/d for acute flares, and 2-3x/wk to recurrent sites to prevent relapses
  - local side effects: stinging, burning, allergic contact dermatitis
  - U.S. black box warning of malignancy risk: rare cases of skin cancer and lymphoma reported; no causal relationship established, warning is discounted by both the Canadian Dermatology Association and the American Academy of Dermatology

### Complications

- infections
  - treatment of infections
  - topical mupirocin, retapamulin, ozenoxacin or fusidic acid (Canada only, not available in US)
  - oral antibiotics (e.g. cloxacillin, cephalexin) for widespread *S. aureus* infections

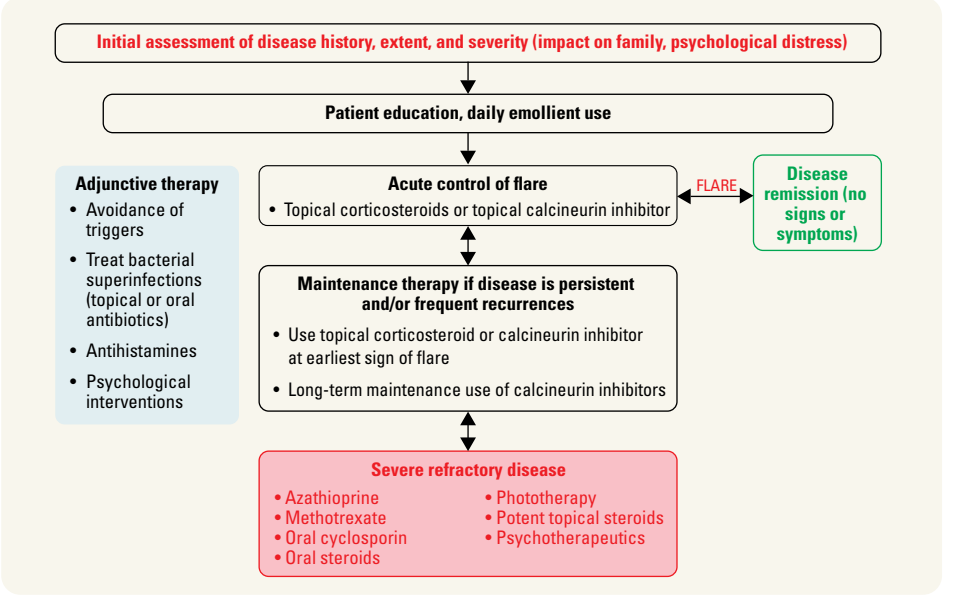



**Figure 5. Atopic dermatitis treatment algorithm**
Adapted from: Ellis C, et al. ICCAD II Faculty. International Consensus Conference on Atopic Dermatitis II (ICCAD II): clinical update and current treatment strategies. Br J Dermatol 2003;148(Suppl 63):3-10

## Contact Dermatitis

### Clinical Feature

- cutaneous inflammation caused by an external agent(s)

**Table 12. Contact Dermatitis**

| | Irritant Contact Dermatitis | Allergic Contact Dermatitis |
|---|---|---|
| **Mechanism of Reaction** | Toxic injury to skin; non-immune mechanism | Cell-mediated delayed (Type IV) hypersensitivity reaction (see Rheumatology, RH2) |
| **Type of Reaction** | Erythema, dryness, fine scale, burning<br>Acute: quick reaction, sharp margins (e.g. from acid/alkali exposure)<br>Cumulative insult: slow to appear, poorly defined margins (e.g. from soap), more common | Erythema with a papulovesicular eruption, swelling, pruritus |
| **Frequency** | Majority; will occur in anyone given sufficient concentration of irritants | Minority; patient acquires susceptibility to allergen that persists indefinitely |
| **Distribution** | Hands are the most common site | Areas exposed to allergen |
| **Examples** | Soaps, weak alkali, detergents, organic solvents, alcohol, oils | Many allergens are irritants, so may coincide with irritant dermatitis |
| **Management** | Avoidance of irritants<br>Wet compresses with Burrow's solution<br>Barrier moisturizers<br>Topical/oral steroids | Patch testing to determine specific allergen<br>Avoid allergen and its cross-reactants<br>Wet compresses soaked in Burrow's solution (drying agent)<br>Topical steroids BID prn<br>Systemic steroids prn if extensive |

# Dyshidrotic Dermatitis

### Clinical Feature
- "tapioca pudding" papulovesicular dermatitis of hands and feet that coalesce into plaques, followed by painful fissuring
- acute stage often very pruritic
- secondary infections common
- lesions heal with desquamation and may lead to chronic lichenification
- sites: palms and soles ± dorsal surfaces of hands and feet

### Pathophysiology
- unknown
- NOT caused by hyperhidrosis (excessive sweating)
- emotional stress may precipitate flares

### Management
- topical: high potency corticosteroid with plastic cling wrap occlusion to increase penetration
- intralesional triamcinolone injection
- systemic
  - prednisone in severe cases
  - alitretinoin (Toctino) for all types of chronic hand dermatitis, including dyshidrotic dermatitis
  - antibiotics for secondary *S. aureus* infection

# Nummular Dermatitis

### Clinical Feature
- nummular (coin-shaped), pruritic, dry, scaly, erythematous plaques
- often associated with atopic and dyshidrotic dermatitis
- secondary infection common

### Pathophysiology
- little is known, but it is often accompanied by xerosis, which results from a dysfunction of the epidermal lipid barrier; this in turn can allow permeation of environmental agents, which can induce an allergic or irritant response

### Management
- moisturization
- mid to high potency corticosteroid ointment twice daily

# Seborrheic Dermatitis

### Clinical Feature
- greasy, erythematous, yellow, scaling, minimally elevated papules and plaques in areas rich in sebaceous glands, can look moist and superficially eroded in flexural regions
- infants: "cradle cap"
- children: may be generalized with flexural and scalp involvement
- adults: diffuse involvement of scalp margin with yellow to white flakes, pruritus, and underlying erythema
- sites: scalp, eyebrows, eyelashes, beard, glabella, post-auricular, over sternum, trunk, body folds, genitalia

### Pathophysiology
- possible etiologic association with *Malassezia* spp. (yeast)

### Epidemiology
- common in infants and adolescents
- increased incidence and severity in immunocompromised patients and Parkinson disease
- in adults can cause dandruff (pityriasis sicca)

### Management
- face: ketoconazole (Nizoral®) cream daily or bid and/or mild steroid cream daily or bid
- scalp: salicylic acid in olive oil or Derma-Smoothe FS® lotion (peanut oil, mineral oil, fluocinolone acetonide 0.01%) to remove dense scales, 2% ketoconazole shampoo (Nizoral®), ciclopirox (Stieprox®) shampoo, selenium sulfide (e.g. Selsun®) or zinc pyrithione (e.g. Head and Shoulders®) shampoo, steroid lotion (e.g. betamethasone valerate 0.1% lotion bid)

## Stasis Dermatitis

### Clinical Feature
- erythematous, scaly, pruritic plaques in lower legs, particularly the medial ankle
- brown hemosiderin deposition, woody fibrosis, atrophy blanche, and lipodermatosclerosis in late stages
- usually bilateral, accompanied by swelling, oozing, crusting, may have accompanying varicosities

### Pathophysiology
- chronic venous insufficiency leads to venous stasis
- surrounding soft tissue inflammation and fibrosis results

### Investigations
- Doppler and colour-coded Duplex sonography if suspicious for DVT
- swab for bacterial culture if there is crusting

### Management
- compression stockings
- rest and elevate legs (above the level of the heart)
- moisturizer to treat xerosis
- mid-high potency topical corticosteroids to control inflammation

### Complications
- ulceration (common at medial malleolus), secondary bacterial infections

## Lichen Simplex Chronicus

### Clinical Feature
- well-defined plaque(s) of lichenified skin with increased skin markings ± excoriations
- common sites: neck, scalp, lower extremities, urogenital area
- often seen in patients with atopy

### Pathophysiology
- skin hyperexcitable to itch, continued rubbing/scratching of skin results
- eventually lichenification occurs

### Investigations
- if patient has generalized pruritus, rule out systemic cause: CBC with differential count, transaminases, bilirubin, renal and thyroid function tests, TSH, glucose, SPEP
- CXR if lymphoma suspected

### Management
- antipruritics (e.g. antihistamines, topical or intralesional glucocorticoids, Unna boot)

# Papulosquamous Diseases

## Lichen Planus



**The 6 Ps of Lichen Planus**
**P**urple
**P**ruritic
**P**olygonal
**P**eripheral
**P**apules
**P**enis (i.e. mucosa)

### Clinical Feature
- acute or chronic inflammation of mucous membranes or skin
- morphology: pruritic, well-demarcated, violaceous, polygonal, flat-topped papules
- common sites: wrists, ankles, mucous membranes in 60% (mouth, vulva, glans), nails, scalp
- distribution: symmetrical and bilateral
- Wickham's striae: reticulate white-grey lines over surface; pathognomonic but may not be present
- mucous membrane lesions: lacy, whitish reticular network, milky-white plaques/papules; increased risk of SCC in erosions and ulcers
- nails: longitudinal ridging; dystrophic; pterygium formation
- scalp: scarring alopecia with perifollicular hyperkeratosis and erythema
- spontaneously resolves but may last for wk, mo or yr (mouth and skin lesions)
- rarely associated with hepatitis C
- Koebner phenomenon

### Pathophysiology
- autoimmune, antigen unknown
- lymphocyte activation leads to keratinocyte apoptosis

### Epidemiology
- 1%, 30-60 yr, F>M

### Investigations
- consider a skin biopsy
- hepatitis C serology if patient has risk factors

### Management
- topical or intralesional corticosteroids
- short courses of oral prednisone (rarely)
- phototherapy or oral retinoids or systemic immunosuppressants (e.g. azathioprine, methotrexate, cyclosporine) for extensive or recalcitrant cases

## Pityriasis Rosea



### Clinical Feature
- acute, self-limiting eruption characterized by red, oval plaques/patches with central scale that does not extend to edge of lesion
- long axis of lesions follows skin tension lines (i.e. Langer's Lines) parallel to ribs producing "Christmas tree" pattern on back
- varied degree of pruritus
- most start with a "herald" patch which precedes other lesions by 1-2 wk
- common sites: trunk, proximal aspects of arms and legs

### Etiology
- suspected HHV-7 or HHV-6 reactivation

### Investigations
- none required

### Management
- none required; clears spontaneously in 6-12 wk
- symptomatic: topical glucocorticoids if pruritic, cool compresses, emollients

## Psoriasis

### Classification
1. plaque psoriasis 2. guttate psoriasis 3. erythrodermic psoriasis
4. pustular psoriasis 5. inverse psoriasis

### Pathophysiology
- not fully understood, genetic and immunologic factors
- shortened keratinocyte cell cycle leads to Th1- and Th17-mediated inflammatory response

### Epidemiology
- 1.5-2%, M=F
- all ages: peaks of onset: 20-30 yr old and 50-60 yr old
- polygenic inheritance: 8% with 1 affected parent, 41% with both parents affected
- risk factors: smoking, obesity, alcohol, drugs, infections, physical trauma (Koebner phenomenon)

### Differential Diagnosis
- AD, mycosis fungoides (cutaneous T-cell lymphoma), seborrheic dermatitis, tinea, nummular dermatitis, lichen planus

### Investigations
- biopsy (if atypical presentation, rarely needed)

### 1. PLAQUE PSORIASIS

### Clinical Feature
- chronic and recurrent disease characterized by well-circumscribed erythematous papules/plaques with silvery-white scales
- often worse in winter (lack of sun)
- Auspitz sign: bleeds from minute points when scale is removed
- common sites: scalp, extensor surfaces of elbows and knees, trunk (especially buttocks), nails, pressure areas

## Management

- depends on severity of disease, as defined by BSA affected or less commonly PASI
- mild (<3% BSA)
  - topical steroids, topical vitamin D3 analogues, or a combination of the two are first line
  - topical retinoid ± topical steroid combination, anthralin, and tar are also effective but tend to be less tolerated than first line therapies
  - emollients
  - phototherapy or systemic treatment may be necessary if the lesions are scattered or if it involves sites that are difficult to treat such as palms, soles, scalp, genitals
- moderate (3-10% BSA) to severe (>10% BSA)
  - goal of treatment is to attain symptom control that is adequate from patient's perspective
  - phototherapy if accessible
  - systemic or biological therapy based on patient's treatment history and comorbidities
  - topical steroid ± topical vitamin D3 analogue as adjunct therapy

**Calcipotriol is a Vitamin D Derivative**
**Dovobet®** = calcipotriene combined with betamethasone dipropionate and is considered to be one of the most potent topical psoriatic therapies

### Table 13. Topical Treatment of Psoriasis

| Treatment | Mechanism | Comments |
|---|---|---|
| **Emollients** | Reduce fissure formation | |
| **Salicylic acid 1-12%** | Remove scales | |
| **Tar (LCD: liquor carbonis detergens)** | Inhibits DNA synthesis, increases cell turnover | Poor long-term compliance |
| **Topical Corticosteroids** | Reduce scaling, redness and thickness | Use appropriate potency steroid in different areas for degree of psoriasis |
| **Vitamin D3 analogues: Calcipotriene / calcipotriol (Dovonex®, Silkis®)** | Reduces keratinocyte hyperproliferation | |
| **Betamethasone + calciprotriene (Dovobet®)** | Combined corticosteroid and vitamin D3 analogue. See above mechanisms | Not to be used on face and folds |
| **Tazarotene (Tazorac®) (gel/cream)** | Retinoid derivative, decreased scaling | Irritating |

### Table 14. Systemic Treatment of Psoriasis

| Treatment | Considerations | Adverse Effects |
|---|---|---|
| **Acitretin** | More effective when used in combination with phototherapy | Alopecia, cheilitis, teratogenicity, hepatotoxicity, photosensitivity, epistaxis, xerosis, hypertriglyceridemia |
| **Cyclosporine** | Used for intermittent control rather than continuously<br>Avoid using for >1 yr | Renal toxicity, hypertension, hypertriglyceridemia, immunosuppression, lymphoma |
| **Methotrexate** | Has been used for over 50 yr | Bone marrow toxicity, hepatic cirrhosis, teratogenicity |
| **Apremilast (Otezla®)** | Extremely safe | GI upset, headache, loose stool, weight loss |
| **PUVA** | Highly effective in achieving remission<br>Avoid >200 sessions in lifetime | Pruritus, burning, skin cancer |
| **UVB and "Narrow band" UVB (311-312 nm)** | UVB much less carcinogenic than PUVA<br>Narrowband has not been shown to increase the risk of skin cancer | Rare burning |

### Table 15. Biologics Approved in Canada

| Treatment | Route | Dosing Schedule | Effectiveness | Action |
|---|---|---|---|---|
| **Etanercept (Enbrel®)*** | SC | 50 mg twice weekly for 3 mo, then 50 mg weekly | +++ | Anti-TNF |
| **Adalimumab (Humira®)*** | SC | 80 mg x 1, then 40 mg at wk 1 and every 2 wk thereafter | ++++ | Anti-TNF |
| **Infliximab (Remicade®)*** | IV | 5 mg/kg at wk 0, 2, 6, and every 8 wk thereafter | +++++ | Anti-TNF |
| **Ustekinumab (Stelara®)** | SC | 45 mg or 90 mg at wk 0, 4, and every 12 wk thereafter | ++++ | Anti-IL 12/23 |
| **Secukinumab (Cosentyx®)** | SC | 300 mg at wk 0, 1, 2, 3, 4, and every 4 wk thereafter | +++++ | Anti-IL 17A |
| **Ixekizumab (Taltz®)** | SC | 160 mg at wk 0, then 80 mg at wk 2, 4, 6, 8, 10, 12, then 80 mg every 4 wk thereafter | +++++ | Anti-IL 17A |
| **Guselkumab (Tremfya®)** | SC | 100 mg at wk 0, 4, and every 8 wk thereafter | +++++ | Anti-IL 23 |
| **Broadalumab (Siliq®)** | SC | 210 mg at wk 0, 1, 2 and every 2 wk thereafter | +++++ | mAb IL-17R (brodalumab is a monoclonal antibody that targets the IL-17 receptor |

*Can also be used to treat psoriatic arthritis

- biologics under study for treatment of psoriasis: risankizumab, tildrakizumab

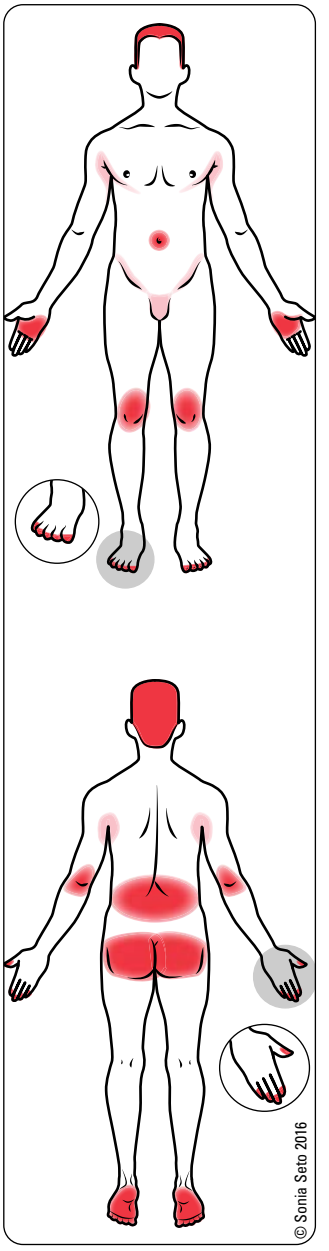



**Figure 6. Psoriasis distribution**

**Mechanism of Biologics**
"-mab" = monoclonal antibody
"-cept" = receptor

### 2. GUTTATE PSORIASIS ("DROP-LIKE")

#### Clinical Feature
- discrete, scattered salmon-pink small scaling papules
- sites: diffuse, usually on trunk and legs, sparing palms and soles
- often antecedent streptococcal pharyngitis

#### Management
- UVB phototherapy, sunlight, lubricants, topical steroids
- penicillin V or erythromycin if Group A β-hemolytic Streptococcus on throat culture

### 3. ERYTHRODERMIC PSORIASIS

#### Clinical Feature
- generalized erythema (>90% of BSA) with fine desquamative scale on surface
- associated signs and symptoms: arthralgia, pruritus, dehydration, electrolyte imbalance
- aggravating factors: lithium, β-blockers, NSAIDs, antimalarials, phototoxic reaction, infection

#### Management
- IV fluids, monitor fluids and electrolytes, may require hospitalization
- treat underlying aggravating condition, sun avoidance
- cyclosporine, acitretin, methotrexate, UV, biologics

### 4. PUSTULAR PSORIASIS



#### Clinical Feature
- sudden onset of erythematous macules and papules which evolve rapidly into pustules, can be painful
- may be generalized or localized
- patient usually has a history of psoriasis; may occur with sudden withdrawal from steroid therapy

#### Management
- methotrexate, cyclosporine, acitretin, UV, biologics

### 5. INVERSE PSORIASIS

#### Clinical Feature
- erythematous plaques on flexural surfaces such as axillae, inframammary folds, gluteal fold, inguinal folds
- lesions may be macerated

#### Management
- low potency topical corticosteroids
- topical vitamin D derivatives (e.g. calcipotriene, calcitriol)
- topical calcineurin inhibitors (e.g. tacrolimus, pimecrolimus)

### 6. PSORIATIC ARTHRITIS
- 20-30% of patients with psoriasis also suffer from psoriatic arthritis
- psoriatic patients with nail or scalp involvement are at a higher risk for developing psoriatic arthritis
- see Rheumatology, RH24

# Vesiculobullous Diseases



## Bullous Pemphigoid



#### Clinical Feature
- chronic autoimmune bullous eruption characterized by pruritic, tense, subepidermal bullae on an erythematous or normal skin base
- can present as urticarial plaques without bullae
- common sites: flexor aspect of forearms, axillae, medial thighs, groin, abdomen, mouth in 33%

#### Pathophysiology
- IgG produced against dermal-epidermal basement membrane proteins (hemidesmosomes) leads to subepidermal bullae

#### Epidemiology
- mean age of onset: 60-80 yr old, F=M

### Investigations
- immunofluorescence shows linear deposition of IgG and C3 along the basement membrane
- anti-basement membrane antibody (IgG) (pemphigoid antibody detectable in serum)

### Prognosis
- heals without scarring, usually chronic
- rarely fatal

### Management
- prednisone 0.5-1 mg/kg/d until clear, then taper ± steroid-sparing agents (e.g. azathioprine, cyclosporine, mycophenolate mofetil)
- topical potent steroids (clobetasol) may be as effective as systemic steroids in limited disease
- tetracycline ± nicotinamide is effective for some cases
- immunosuppressants such as azathioprine, mycophenolate mofetil, cyclosporine
- IVIg and plasmapheresis for refractory cases

## Pemphigus Vulgaris





**Pemphigus Vulgaris vs. Bullous Pemphigoid**
Vulgari**S** = **S**uperficial, intraepidermal, flaccid lesions
Pemphigoi**D** = **D**eeper, tense lesions at the dermal-epidermal junction



**Pemphigus Foliaceus**
An autoimmune intraepidermal blistering disease that is more superficial than pemphigus vulgaris due to antibodies against desmoglein-1, a transmembrane adhesion molecule. Appears as crusted patches, erosions and/or flaccid bullae that usually start on the trunk. Localized disease can be managed with topical steroids. Active widespread disease is treated like pemphigus vulgaris

### Clinical Feature
- autoimmune blistering disease characterized by flaccid, non-pruritic intraepidermal bullae/vesicles on an erythematous or normal skin base
- may present with erosions and secondary bacterial infection
- sites: mouth (90%), scalp, face, chest, axillae, groin, umbilicus
- Nikolsky's sign: epidermal detachment with shear stress
- Asboe-Hansen sign: pressure applied to bulla causes it to extend laterally

### Pathophysiology
- IgG against epidermal desmoglein-1 and -3 lead to loss of intercellular adhesion in the epidermis

### Epidemiology
- 40-60 yr old, M=F, higher prevalence in Jewish, Mediterranean, Asian populations
- paraneoplastic pemphigus may be associated with thymoma, myasthenia gravis, malignancy, and use of D-penicillamine

### Investigations
- immunofluorescence: shows IgG and C3 deposition intraepidermally
- circulating serum anti-desmoglein IgG antibodies

### Prognosis
- lesions heal with hyperpigmentation but do not scar
- may be fatal unless treated with immunosuppressive agents

### Management
- prednisone 1-2 mg/kg until no new blisters, then 1-1.5 mg/kg until clear, then taper ± steroid-sparing agents (e.g. azathioprine, cyclophosphamide, cyclosporine, IVIg, mycophenolate mofetil, rituximab)

## Dermatitis Herpetiformis

### Clinical Feature
- grouped papules/vesicles/urticarial wheals on an erythematous base, associated with intense pruritus, burning, stinging, excoriations
- lesions grouped, bilaterally symmetrical
- common sites: extensor surfaces of elbows/knees, sacrum, buttocks, scalp

### Pathophysiology
- transglutaminase IgA deposits in the skin alone or in immune complexes leading to eosinophil and neutrophil infiltration
- 90% have HLA B8, DR3, DQWZ
- 90-100% associated with an often subclinical gluten-sensitive enteropathy (i.e. celiac disease)
- 30% have thyroid disease; increased risk of intestinal lymphoma in untreated comorbid celiac disease; iron/folate deficiency is common

### Epidemiology
- 20-60 yr old, M:F = 2:1

### Investigations
- biopsy
- immunofluorescence shows IgA deposits in perilesional skin

### Management
- dapsone (sulfapyridine if contraindicated or poorly tolerated)
- gluten-free diet for life – this can reduce risk of lymphoma

# Porphyria Cutanea Tarda

### Clinical Feature
- skin fragility followed by formation of tense vesicles/bullae and erosions on photoexposed skin
- gradual healing to scars, milia
- periorbital violaceous discolouration, diffuse hypermelanosis, facial hypertrichosis
- common sites: light-exposed areas subjected to trauma, dorsum of hands and feet, nose, and upper trunk

### Pathophysiology
- uroporphyrinogen decarboxylase deficiency leads to excess heme precursors
- can be associated with hemochromatosis, alcohol abuse, DM, drugs (estrogen therapy, NSAIDs), HIV, hepatitis C, increased Fe indices

### Epidemiology
- 30-40 yr old, M>F

### Investigations
- urine and 5% HCl shows orange-red fluorescence under Wood's lamp (UV rays)
- 24 h urine has elevated uroporphyrins
- stool contains elevated coproporphyrins
- immunofluorescence shows IgE at dermal-epidermal junctions

### Management
- discontinue aggravating substances (alcohol, estrogen therapy)
- phlebotomy to decrease body iron load
- low dose hydroxychloroquine

# Drug Eruptions

## Exanthematous

### EXANTHEMATOUS DRUG REACTION

### Clinical Feature
- morphology: erythematous macules and papules ± scale
- spread: symmetrical, trunk to extremities
- time course: 7-14 d after drug initiation, fades 7-14 d after withdrawal

### Epidemiology
- most common cutaneous drug reaction; increased in presence of infections
- common causative agents: penicillin, sulfonamides, phenytoin

### Management
- weigh risks and benefits of drug discontinuation
- antihistamines, emollients, topical steroids

**Diagnosis of a Drug Reaction**

Classification by Naranjo et. al has 4 criteria:
1. Temporal relationship between drug exposure and reaction
2. Recognized response to suspected drug
3. Improvement after drug withdrawal
4. Recurrence of reaction on re-challenge with the drug

Definite drug reaction requires all 4 criteria to be met
Probable drug reaction requires #1-3 to be met
Possible drug reaction requires only #1

### DRUG INDUCED HYPERSENSITIVITY SYNDROME (DIHS) / DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)

### Clinical Feature
- morphology: morbilliform rash involving face, trunk, arms; can have facial edema
- systemic features: fever, malaise, cervical lymphadenopathy, internal organ involvement (e.g. hepatitis, arthralgia, nephritis, pneumonitis, lymphadenopathy, hematologic abnormalities, thyroid abnormalities)
- spread: starts with face or periorbitally and spreads caudally; no mucosal involvement
- time course: onset 1-6 wk after first exposure to drug; persists wk after withdrawal of drug

**Drug Hypersensitivity Syndrome Triad**
- Fever
- Exanthematous eruption
- Internal organ involvement

### Epidemiology
- rare: incidence varies considerably depending on drug
- common causative agents: anticonvulsants (e.g. phenytoin, phenobarbital, carbamazepine, lamotrigine), sulfonamides, and allopurinol
- 10% mortality if severe, undiagnosed, and untreated

### Management
- discontinue offending drug ± prednisone 0.5mg/kg/d, consider cyclosporine in severe cases
- may progress to generalized exfoliative dermatitis/erythroderma if drug is not discontinued

# Urticarial

## DRUG INDUCED URTICARIA AND ANGIOEDEMA

### Clinical Feature
- morphology: wheals lasting >24 h unlike non-drug induced urticaria, angioedema (face and mucous membranes)
- systemic features: may be associated with systemic anaphylaxis (bronchospasm, laryngeal edema, shock)
- time course: h-d after exposure depending on the mechanism

### Epidemiology
- second most common cutaneous drug reaction
- common causative agents: penicillins, ACEI, analgesics/anti-inflammatories, radiographic contrast media

### Management
- discontinue offending drug, treatment with antihistamines, steroids, epinephrine if anaphylactic

## SERUM SICKNESS-LIKE REACTION

### Clinical Feature
- morphology: symmetrical cutaneous eruption (usually urticarial)
- systemic features: malaise, low grade fever, arthralgia, lymphadenopathy
- time course: appears 1-3 wk after drug initiation, resolve 2-3 wk after withdrawal

### Epidemiology
- more prevalent in kids (0.02-0.2%)
- common causative agents: cefaclor in kids; bupropion in adults

### Management
- discontinue offending drug ± topical/oral corticosteroids

# Pustular

## ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS (AGEP)

### Clinical Feature
- morphology: extensive erythematous, edematous, and sterile pustules
- systemic features: high fever, leukocytosis with neutrophilia
- spread: starts in face and intertriginous areas, spreads to trunk and extremities
- time course: appears 1 wk after drug initiation, resolves 2 wk after withdrawal

### Epidemiology
- rare: 1-5/million
- common causative agents: aminopenicillins, cephalosporins, clindamycin, calcium channel blockers

### Management
- discontinue offending drug and systemic corticosteroids

# Bullous



## STEVEN-JOHNSON SYNDROME (SJS)/TOXIC EPIDERMAL NECROLYSIS (TEN)

### Clinical Feature
- morphology: prodromal rash (morbilliform/targetoid lesions ± purpura, or diffuse erythema), confluence of flaccid blisters, positive Nikolsky sign (epidermal detachment with shear stress), full thickness epidermal loss; dusky tender skin, bullae, desquamation/skin sloughing, atypical targets
- classification: BSA with epidermal detachment: <10% in SJS, 10-30% in SJS/TEN overlap, and >30% in TEN
- spread: face and extremities; may generalize; scalp, palms, soles relatively spared; erosion of mucous membranes (lips, oral mucosa, conjunctiva, GU mucosa)
- systemic features: fever (higher in TEN), cytopenias, renal tubular necrosis/AKI, tracheal erosion, infection, contractures, corneal scarring, phimosis, vaginal synechiae
- time course: appears 1-3 wk after drug initiation; progression <4 d; epidermal regrowth in 3 wk
- can have constitutional symptoms: malaise, fever, hypotension, tachycardia

### Epidemiology
- SJS: 1.2-6/million; TEN: 0.4-1.2/million
- risk factors: SLE, HIV/AIDS, HLA-B1502 (reaction most prevalent in East Asians, associated with carbamazepine), HLA-B5801 (reaction most prevalent in Asians and Caucasians, associated with allopurinol)
- common causative agents: drugs (allopurinol, anti-epileptics, sulfonamides, NSAIDs, cephalosporins) responsible in 50% of SJS and 80% of TEN; viral or mycoplasma infections
- prognosis: 5% mortality in SJS, 30% in TEN due to fluid loss and infection



**SCORTEN Score for TEN Prognosis**
One point for each of: age ≥40, malignancy, body surface area detached ≥10%, tachycardia ≥120 bpm, serum urea >10 mmol/L, serum glucose >14 mmol/L, serum bicarbonate <20 mmol/L

Used to determine appropriate clinical setting: score 0-1 can be treated in non-specialized wards; score ≥2 should be transferred to intensive care or burn unit

Score at admission is predictive of survival: 94% for 0-1, 87% for 2, 53% for 3, 25% for 4, and 17% for ≥5

### Differential Diagnosis
- scarlet fever, phototoxic eruption, GVHD, SSSS, exfoliative dermatitis, AGEP, paraneoplastic pemphigus

### Management
- discontinue offending drug
- admit to intermediate/intensive care/burn unit
- supportive care: IV fluids, electrolyte replacement, nutritional support, pain control, wound care, sterile handling, monitor for and treat infection
- IVIg or cyclosporine or etanercept



**Systemic Immunomodulating Therapies for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Systematic Review and Meta-analysis**
JAMA Dermatol 2017;153:514-22.
**Purpose**: To examine possible immunomodulating treatments for SJS/TEN and estimate mortality effect compared to supportive care.
**Methods**: Systematic review of randomized and nonrandomized studies on systemic immunomodulating therapies or supportive care for SJS/TEN.
**Results**: Ninety-six studies with 3248 patients were included in the final analysis. Glucocorticoids were associated with a survival benefit for patients (aggregate - OR 0.5, 95% CI 0.3-1.01). Though findings were limited to a small number of patients overall, cyclosporine was associated with significant benefit (unstratified iPD model – OR 0.1; 95% CI 0.0-0.4). No beneficial effects were observed with other therapies, including intravenous immunoglobulins.
**Conclusion**: Though based on limited evidence, glucocorticoids and cyclosporine were most promising as SJS/TEN immunomdulating therapies.

# Other

## FIXED DRUG ERUPTION

### Clinical Feature
- morphology: sharply demarcated erythematous oval patches on the skin or mucous membranes
- spread: commonly face, mucosa, genitalia, acral; recurs in same location upon subsequent exposure to the drug (fixed location)

### Epidemiology
- common causative agents: antimicrobials (tetracycline, sulfonamides), anti-inflammatories, psychoactive agents (barbiturates), phenolphthalein

### Management
- discontinue offending drug ± prednisone 1mg/kg/d x 2 wk for generalized lesions ± potent topical corticosteroids for non-eroded lesions or antimicrobial ointment for eroded lesions

## PHOTOSENSITIVITY REACTION

### Clinical Feature
- phototoxic reaction: "exaggerated sunburn" (erythema, edema, vesicles, bullae) confined to sun-exposed areas
- photoallergic reaction: pruritic eczematous eruption with papules, vesicles, scaling, and crusting that may spread to areas not exposed to light

### Pathophysiology
- phototoxic reaction: direct tissue injury
- photoallergic reaction: type IV delayed hypersensitivity

### Epidemiology
- common causative agents: chlorpromazine, doxycycline, thiazide diuretics, procainamide

### Management
- sun protection ± topical/oral corticosteroids

# Heritable Disorders

# Ichthyosis Vulgaris

### Clinical Feature
- xerosis with fine scaling as well as large adherent scales ("fish-scales")
- affects arms, legs, palms, soles, back, forehead, and cheeks; spares flexural creases
- improves in summer, with humidity, and as the child grows into adulthood

### Pathophysiology
- genetic deficiency in filaggrin protein leads to abnormal retention of keratinocytes (hyperkeratosis)
- scaling without inflammation

### Epidemiology
- 1:300 incidence
- autosomal dominant inheritance
- associated with AD and keratosis pilaris

### Investigations
- electron microscopy: keratohyalin granules

### Management
- immersion in bath and oils followed by an emollient cream, humectant cream, or creams/oil containing urea or α- or β-hydroxy acids
- intermittent systemic retinoids for severe cases

# Neurofibromatosis (Type I; von Recklinghausen's Disease)

### Clinical Feature
- diagnostic criteria includes 2 or more of the following:
  1. more than 5 café-au-lait patches >1.5 cm in an adult or more than 5 café-au-lait macules >0.5 cm in a child <5 yr
  2. axillary or inguinal freckling
  3. iris hamartomas (Lisch nodules)
  4. optic gliomas
  5. neurofibromas
  6. distinctive bony lesion (sphenoid wing dysplasia or thinning of long bone cortex)
  7. first degree relative with neurofibromatosis Type 1
- associated with pheochromocytoma, astrocytoma, bilateral acoustic neuromas, bone cysts, scoliosis, precocious puberty, developmental delay, and renal artery stenosis
- skin lesions less prominent in neurofibromatosis Type II (see Pediatrics, P79)

### Pathophysiology
- autosomal dominant disorder with excessive and abnormal proliferation of neural crest elements (Schwann cells, melanocytes), high incidence of spontaneous mutation
- linked to absence of neurofibromin (a tumour suppressor gene)

### Epidemiology
- incidence 1:3000

### Investigations
- Wood's lamp to detect café-au-lait macules in patients with pale skin

### Management
- refer to orthopedics, ophthalmology, plastics, and psychology
- follow-up annually for brain tumours (e.g. astrocytoma)
- excise suspicious or painful lesions
- see Pediatrics, P79

# Vitiligo

### Clinical Feature
- primary pigmentary disorder characterized by depigmentation
- acquired destruction of melanocytes characterized by sharply marginated white patches
- associated with streaks of depigmented hair, chorioretinitis
- sites: extensor surfaces and periorificial areas (mouth, eyes, anus, genitalia)
- Koebner phenomenon, may be precipitated by trauma

### Pathophysiology
- acquired autoimmune destruction of melanocytes

### Epidemiology
- 1% incidence, polygenic
- 30% with positive family history

### Investigations
- rule out associated autoimmune diseases: thyroid disease, pernicious anemia, Addison's disease, Type I DM
- Wood's lamp to detect lesions: illuminates UV light onto skin to detect amelanosis (porcelain white discolouration)

### Management
- sun avoidance and protection
- topical calcineurin inhibitor (e.g. tacrolimus, pimecrolimus) or topical corticosteroids
- PUVA or NB-UVB
- make-up
- "bleaching" normal pigmented areas (i.e. monobenzyl ether of hydroquinone 20%) if widespread loss of pigmentation



**Interventions for Vitiligo**
Cochrane Database Syst Rev 2015;2:CD003263
**Purpose**: To assess the effects of existing interventions used in the management of vitiligo.
**Study**: Systematic review of RCTs assessing the effects of vitiligo treatments (topical treatments, light therapies, oral treatments, surgical methods). Primary outcomes were quality of life and >75% re-pigmentation adverse effects.
**Results**: Ninety-six RCTs with 4512 participants were deemed eligible, of which only 25 reported on the primary outcomes and were finally included. Re-pigmentation was better with combination therapy (calcipotriol plus PUVA, than PUVA alone, hydrocortisone-17-butyrate plus excimer laser vs. excimer laser alone; oral minipulse of prednisolone (OMP) plus narrowband UVB (NB-UVB) vs. OMP alone; azathioprine with PUVA vs. PUVA alone; 8-methoxypsoralen (8-MOP) plus sunlight versus psoralen). A non-significant increase in proportion of participants with >75% re-pigmentation was noted in favour of NB-UVB compared to PUVA. Compared to PUVA, the NV-UVB group reported lower incidences of nausea and erythema, but not itching.
**Conclusions**: Some studies support existing therapies for vitiligo management, but follow-up is needed to assess permanence of re-pigmentation and higher quality RCTs need to be conducted.

# Infections

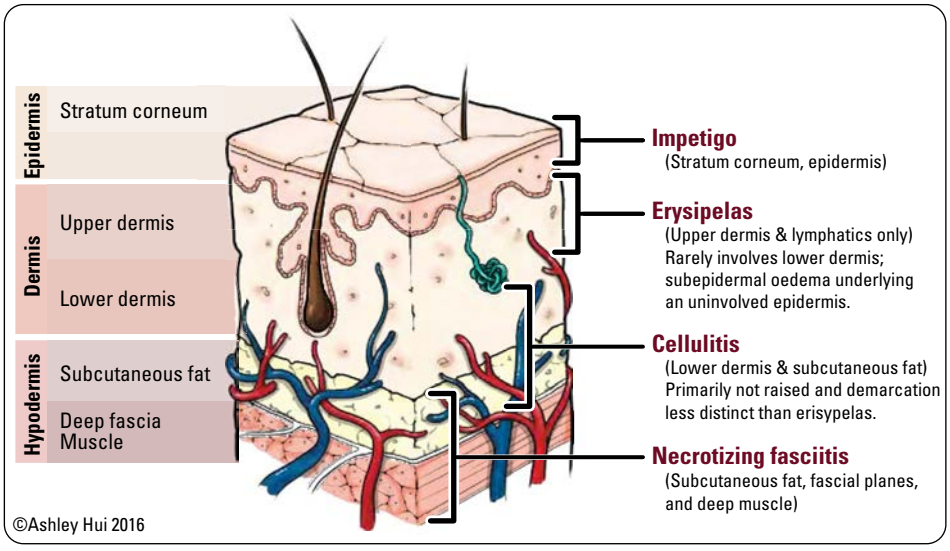



**Figure 7. Layers of skin affected by bacterial infections**

**Location Matters!**

**e.g. Group A Strep Infections**
- Impetigo → just below stratum corneum
- Erysipelas → epidermis and upper dermis only
- Cellulitis → primarily lower dermis and subcutis (primarily not raised, and demarcation less distinct than erysipelas)
- Necrotizing fasciitis → deep fascia and muscle

## Bacterial Infections

### EPIDERMIS

### IMPETIGO

#### Clinical Feature
- acute purulent infection which appears vesicular; progresses to golden yellow "honey-crusted" lesions surrounded by erythema
- can present with bullae
- common sites: face, arms, legs, and buttocks

#### Etiology
- GAS, *S. aureus*, or both

#### Epidemiology
- preschool and young adults living in crowded conditions, poor hygiene, neglected minor trauma

#### Differential Diagnosis
- infected eczema, HSV, VZV

#### Investigations
- Gram stain and culture of lesion fluid or biopsy

#### Management
- remove crusts, use saline compresses, and topical antiseptic soaks bid
- topical antibacterials (e.g. 2% mupirocin or fusidic acid (Canada only) tid; continue for 7-10 d after resolution)
- systemic antibiotics (e.g. cloxacillin or cephalexin for 7-10 d)

## DERMIS

### Table 16. Comparison of Erysipelas and Cellulitis

| | Clinical Feature | Etiology | Complications | Differential Diagnosis | Investigations | Management |
|---|---|---|---|---|---|---|
| **Erysipelas** | Involves upper dermis<br>Confluent, erythematous, sharp raised edge, warm plaque, well demarcated<br>Very painful ("St. Anthony's fire")<br>Sites: face and legs<br>Systemic symptoms: fever, chills, headache, weakness (if present, sign of more serious infection) | GAS | Scarlet fever, streptococcal gangrene, fat necrosis, coagulopathy<br>Spreads via lymphatics | DVT (less red, less hot, smoother), superficial phlebitis, contact dermatitis, photosensitivity reaction, stasis dermatitis, panniculitis, vasculitis | Clinical diagnosis: rarely do skin/blood culture<br>If suspect necrotizing fasciitis: do immediate biopsy and frozen section, histopathology | 1st line: penicillin, cloxacillin or cefazolin<br>2nd line: clindamycin or cephalexin<br>If allergic to penicillin, use erythromycin |
| **Cellulitis** | Involves lower dermis/subcutaneous fat<br>Unilateral erythematous flat lesion, often with vesicles poorly demarcated, not uniformly raised<br>Tender<br>Sites: commonly on legs<br>Systemic symptoms (uncommon): fever, leukocytosis, lymphadenopathy | GAS, *S. aureus* (large sized wounds), *H. influenzae* (periorbital), *Pasteurella multocida* (dog/cat bite) | Uncommon | Same as erysipelas | Same as erysipelas | 1st line: cloxacillin or cefazolin/cephalexin<br>2nd line: erythromycin or clindamycin<br>Children: cefuroxime<br>If DM (foot infections): TMP/SMX and metronidazole |

## COMMON HAIR FOLLICLE INFECTIONS

### Table 17. Comparison of Superficial Folliculitis, Furuncles, and Carbuncles

| | Clinical Feature | Etiology | Management |
|---|---|---|---|
| **Superficial Folliculitis** | Superficial infection of the hair follicle (versus pseudofolliculitis: inflammation of follicle due to friction, irritation, or occlusion)<br>Acute lesion consists of a dome-shaped pustule at the mouth of hair follicle<br>Pustule ruptures to form a small crust<br>Sites: primarily scalp, shoulders, anterior chest, upper back, other hair-bearing areas | Normal non-pathogenic bacteria (*Staphylococcus* – most common; *Pseudomonas* – hot tub)<br>*Pityrosporum* | Antiseptic (Hibiclens®)<br>Topical antibacterial (fusidic acid, mupirocin, erythromycin, or clindamycin)<br>Oral cloxacillin for 7-10 d |
| **Furuncles (Boils)** | Red, hot, tender, inflammatory nodules with central yellowish point, which forms over summit and ruptures<br>Involves subcutaneous tissue that arises from a hair follicle<br>Sites: hair-bearing skin (thigh, neck, face, axillae, perineum, buttocks) | *S. aureus* | Incise and drain large furuncles to relieve pressure and pain<br>If afebrile: hot wet packs, topical antibiotic<br>If febrile/cellulitis: culture blood and aspirate pustules (Gram stain and C&S)<br>Cloxacillin for 1-2 wk (especially for lesions near external auditory canal/nose, with surrounding cellulitis, and not responsive to topical therapy) |
| **Carbuncles** | Deep-seated abscess formed by multiple coalescing furuncles<br>Usually in areas of thicker skin<br>Occasionally ulcerates<br>Lesions drain through multiple openings to the surface<br>Systemic symptoms may be associated | *S. aureus* | Same as for furuncles |

# Dermatophytoses

### Clinical Feature
- infection of skin, hair, and nails caused by dermatophytes (fungi that live within the epidermal keratin or hair follicle and do not penetrate into deeper structures)

### Pathophysiology
- digestion of keratin by dermatophytes results in scaly skin, broken hairs, crumbling nails/onycholysis

### Etiology
- Trichophyton, Microsporum, Epidermophyton species (Pityrosporum is a superficial yeast and not a dermatophyte)

### Investigations
- skin scrapings, hair, and/or nail clippings analyzed with potassium hydroxide (KOH) prep to look for hyphae and mycelia

### Management
- topicals as first line agents for tinea corporis/cruris and tinea pedis (interdigital type): clotrimazole, or terbinafine or ciclopirox olamine cream applied bid
- oral therapy is indicated for onychomycosis or tinea capitis: terbinafine (Lamisil® – liver toxicity, CYP2D6 inhibitor) or itraconazole (Sporanox® – CYP3A4 inhibitor, liver toxicity)

**A Placebo-Controlled Trial of Antibiotics for Smaller Skin Abscesses**
N Engl J Med 2017;376:2545-55
**Purpose**: To determine the appropriate management of uncomplicated skin abscesses.
**Study**: Multi-centre, prospective, double-blind trial involving outpatient adults and children with abscesses 5 cm or smaller, stratified by presence of surgically drainable abscess, abscess size, number of sites of skin infection, and presence of non-purulent cellulitis. Following incision and drainage, participants were randomly assigned to 10 d courses of clindamycin, TMP-SMX or placebo. Primary outcome was clinical cure 7 to 10 d after treatment end. Intention-to-treat analyses were conducted.
**Results**: Seven hundred and eighty-six participants were enrolled (505 adults, 281 children). Ten d after therapy, the cure rate was similar between clindamycin and TMP-SMX (83.1% vs. 81.7%; p=0.73), and was higher than that of the placebo group (68.9%; p=0.001 for both comparisons). Among those who were cured, new infections at 1 mo follow-up were less common in the clindamycin group than the TMP-SMX or placebo groups (6.8% vs. 11.1%; p=0.03 vs. 12.4%; p=0.06). Adverse events were more frequent with clindamycin than either of the other groups (21.9% s. 11.1% vs. 12.5%), though all resolved without sequelae.
**Conclusions**: Clindamycin or TMP-SMX in conjunction with incision and drainage for simple abscesses improves short-term outcomes compared to incision and drainage alone, though side-effects must be considered.

**Table 18. Different Manifestations of Dermatophyte Infection**

| | Clinical Feature | Differential Diagnosis | Investigations | Management |
|---|---|---|---|---|
| **Tinea Capitis** | Round, scaly patches of alopecia, possibly with broken off hairs; pruritic<br>Sites: scalp, eyelashes, and eyebrows; involving hair shafts and follicles<br>Kerion (boggy, elevated, purulent inflamed nodule/plaque) may form secondary to infection by bacteria and result in scarring<br>May have occipital lymphadenopathy<br>Affects children (mainly black), immunocompromised adults<br>Very contagious and may be transmitted from barber, hats, theatre seats, pets | Alopecia areata, psoriasis, seborrheic dermatitis, trichotillomania | Wood's light examination of hair: green fluorescence only for Microsporum infection<br>Culture of scales/hair shaft<br>Microscopic examination of KOH preparation of scales or hair shafts | Terbinafine (Lamisil®) x 4 wk<br>NB: oral agents are required to penetrate the hair root where dermatophyte resides<br>Adjunctive antifungal shampoos or lotions may be helpful, and may prevent spread (e.g. selenium sulfide, ketoconozole, ciclopirox) |
| **Tinea Corporis** (Ringworm) | Pruritic, scaly, round/oval plaque with active erythematous margin, ± central clearing<br>Sites: trunk, limbs, face | Granuloma annulare, pityriasis rosea, psoriasis, seborrheic dermatitis | Microscopic examinations of KOH prep of scales shows hyphae<br>Culture of scales | Topicals: 1% clotrimazole, 2% ketoconazole<br>2% miconazole, terbinafine or ciclopirox olamine cream bid for 2-4 wk<br>Oral terbinafine, or itraconazole, or fluconazole, or ketoconazole if extensive |
| **Tinea Cruris** ("Jock Itch") | Scaly patch/plaque with a well-defined, curved border and central clearing<br>Pruritic, erythematous, dry/macerated<br>Sites: starts medial thigh, spreads centrifugally to perineum, gluteal cleft, buttocks | Candidiasis (involvement of scrotum and satellite lesions), contact dermatitis, erythrasma | Same as for tinea corporis | Same as for tinea corporis |
| **Tinea Pedis** (Athlete's Foot) | Pruritic scaling and/or maceration of the web spaces, and powdery scaling of soles<br>Acute infection: interdigital (especially 4th web space) red/white scales, vesicles, bullae, often with maceration<br>Secondary bacterial infection may occur<br>Chronic: non-pruritic, pink, scaling keratosis on soles, and sides of feet<br>May present as flare-up of chronic tinea pedis<br>Predisposing factors: heat, humidity, occlusive footwear | AD, contact dermatitis, dyshidrotic dermatitis, erythrasma, intertrigo, inverse psoriasis | Same as for tinea corporis | Same as for tinea corporis |
| **Tinea Manuum** | Primary fungal infection of the hand is rare; usually associated with tinea pedis<br>Acute: blisters at edge of red areas on hands<br>Chronic: single dry scaly patch | AD, contact dermatitis, granuloma annulare, psoriasis | Same as for tinea corporis | Same as for tinea corporis |
| **Tinea Unguium** (Onychomycosis) | Crumbling, distally dystrophic nails; yellowish, opaque with subungual hyperkeratotic debris<br>Toenail infections usually precede fingernail infections<br>*T. rubrum* (90% of all toenail infections) | Psoriasis, lichen planus, contact dermatitis, traumatic onychodystrophies, bacterial infection | Microscopic examinations of KOH prep of scales from subungual scraping shows hyphae<br>Culture of subungual scraping or nail clippings on Sabouraud's agar<br>PAS stain of nail clipping by pathology | Terbinafine (Lamisil®) (6 wk for fingernails, 12 wk for toenails)<br>Itraconazole (Sporanox®) 7 d on, 3 wk off (2 pulses for fingernails, 3 pulses for toenails)<br>Topical: ciclopirox (Penlac®); nail lacquer (often ineffective), Efinaconazole (Jublia®) (48 wk) |

# Parasitic Infections

## SCABIES

### Clinical Feature

- characterized by superficial burrows, intense pruritus (especially nocturnal), and secondary infection
- primary lesion: superficial linear burrows; inflammatory papules and nodules in the axilla and groin
- secondary lesion: small urticarial crusted papules, eczematous plaques, excoriations
- common sites: axillae, groin, buttocks, hands/feet (especially web spaces), sparing of head and neck (except in infants)

### Pathophysiology

- scabies mite remains alive 2-3 d on clothing/sheets
- incubation of 1 mo, then pruritus begins
- re-infection followed by hypersensitivity in 24 h

### Etiology

- *Sarcoptes scabiei* (a mite)
- risk factors: sexual promiscuity, crowding, poverty, nosocomial, immunocompromised

### Differential Diagnosis
- asteatotic eczema, dermatitis herpetiformis, lichen simplex chronicus (neurodermatitis)

### Investigations
- microscopic examination of root and content of burrow and mineral oil mount for mite, eggs, feces
- skin biopsy may sometimes show scabies mite

### Management
- bathe, then apply permethrin 5% cream (i.e. Nix®) from neck down to soles of feet (must be left on for 8-14 h and requires second treatment 7 d after first treatment)
- change underwear and linens; wash twice with detergent in hot water cycle then machine dry
- treat family and close contacts
- pruritus may persist for 2-3 wk after effective treatment due to prolonged hypersensitivity reaction
- mid potency topical steroids and antihistamines for symptom management

## LICE (PEDICULOSIS)

### Clinical Feature
- intensely pruritic, red excoriations, morbilliform rash, caused by louse (a parasite)
- scalp lice: nits (i.e. louse eggs) on hairs; red, excoriated skin with secondary bacterial infection, lymphadenopathy
- pubic lice: nits on hairs; excoriations
- body lice: nits and lice in seams of clothing; excoriations and secondary infection mainly on shoulders, belt-line, and buttocks

### Etiology
- *Phthirus pubis* (pubic), *Pediculus humanus capitis* (scalp), *Pediculus humanus humanus* (body): attaches to body hair and feeds on the nearby body site
- can transmit infectious agents (e.g. *Bartonella Quintana, Rickettsia prowazekii*)

### Differential Diagnosis
- bacterial infection of scalp, seborrheic dermatitis

### Diagnosis
- lice visible on inspection of affected area or clothing seams

### Management
- permethrin 1% (Nix® cream rinse) (ovicidal) or permethrin 1% (RC & Cor®, Kwellada-P® shampoo)
- comb hair with fine-toothed comb using dilute vinegar solution to remove nits
- repeat in 7 d after first treatment
- shave hair if feasible, change clothing and linens; wash with detergent in hot water cycle then machine dry

## BED BUGS (HEMIPTERA)

### Clinical Feature
- burning wheals, turning to firm papules, often in groups of three – "breakfast, lunch and dinner" – in areas with easy access (face, neck, arms, legs, hands)

### Etiology
- caused by Cimex lectularius, a small insect that feeds mainly at night (hides in crevices in walls and furniture during the day)

### Differential Diagnosis
- dermatitis herpetiformis, drug eruptions, ecthyma, other insect bites, scabies

### Investigations
- none required, but lesional biopsy can confirm insect bite reaction

### Management
- professional fumigation
- topical steroids and oral H1-antagonists for symptomatic relief
- definitive treatment is removal of clutter in home and application of insecticides to walls and furniture

# Viral Infections

## HERPES SIMPLEX

### Clinical Feature
- herpetiform (i.e. grouped) vesicles on an erythematous base on skin or mucous membranes
- transmitted via contact with erupted vesicles or via asymptomatic viral shedding
- primary
  - children and young adults
  - usually asymptomatic; may have high fever, regional lymphadenopathy, malaise
  - followed by antibody formation and latency of virus in dorsal nerve root ganglion
- secondary
  - recurrent form seen in adults; much more common than primary
  - prodrome: tingling, pruritus, pain
  - triggers for recurrence: fever, excess sun exposure, physical trauma, menstruation, emotional stress, URTI
- complications: dendritic corneal ulcer, EM, herpes simplex encephalitis (infants at risk), HSV infection on AD causing Kaposi's varicelliform eruption (eczema herpeticum)
- two biologically and immunologically different subtypes: HSV-1 and HSV-2
  - HSV-1
    - typically "cold sores" (grouped vesicles at the mucocutaneous junction which quickly burst)
    - recurrent on face, lips, and hard palate, but NOT on soft, non-keratinized mucous membranes (unlike aphthous ulcers)
  - HSV-2
    - usually sexually transmitted; incubation 2-20 d
    - gingivostomatitis: entire buccal mucosa involved with erythema and edema of gingiva
    - vulvovaginitis: edematous, erythematous, extremely tender, profuse vaginal discharge
    - urethritis: watery discharge in males
    - recurrent on vulva, vagina, penis for 5-7 d
    - differential diagnosis of genital ulcers: Candida balanitis, chancroid, syphilitic chancres

Both HSV-1 and HSV-2 can occur on face or genitalia

### Investigations
- Tzanck smear with Giemsa stain shows multinucleated giant epithelial cells
- viral culture, electron microscopy, and direct fluorescence antibody test of specimen taken from the base of a relatively new lesion
- serologic testing for antibody for current or past infection if necessary

### Management
- HSV-1
  - treat during prodrome to prevent vesicle formation
  - topical antiviral (Zovirax®/Xerese®) cream, apply 5-6x/d x 4-7 d for facial/genital lesions
  - oral antivirals (e.g. acyclovir, famciclovir, valacyclovir) are far more effective and have an easier dosing schedule than topicals
- HSV-2
  - rupture vesicle with sterile needle if you wish to culture it
  - wet dressing with aluminum subacetate solution, Burow's compression, or betadine solution
  - 1st episode: acyclovir 200 mg PO 5x/d x 10 d
    - maintenance: acyclovir 400 mg PO bid
  - famciclovir and valacyclovir may be substituted and have better enteric absorption and less frequent dosing
  - in case of herpes genitalis, look for and treat any other STIs
  - for active lesions in pregnancy, see Obstetrics, OB29

**Erythema Multiforme**
**Etiology**: most often HSV or mycoplasma pneumoniae, rarely drugs
**Morphology**: macules/papules with central vesicles; classic bull's-eye pattern of concentric light and dark rings (typical target lesions)
**Management**: symptomatic treatment (oral antihistamines, oral antacids); corticosteroids in severely ill (controversial); prophylactic oral acyclovir for 6-12 mo for HSV-associated EM with frequent recurrences

## HERPES ZOSTER (SHINGLES)

### Clinical Feature
- unilateral dermatomal eruption occurring 3-5 d after pain and paresthesia of that dermatome
- vesicles, bullae, and pustules on an erythematous, edematous base
- lesions may become eroded/ulcerated and last days to weeks
- pain can be pre-herpetic, synchronous with rash, or post-herpetic
- severe post-herpetic neuralgia often occurs in elderly
- Hutchinson's sign: shingles on the tip of the nose signifies ocular involvement
  - shingles in this area involves the nasociliary branch of the ophthalmic branch of the trigeminal nerve (V1)
- distribution: thoracic (50%), trigeminal (10-20%), cervical (10-20%); disseminated in HIV

Herpes zoster typically involves a single dermatome; lesions rarely cross the midline

### Etiology
- caused by reactivation of VZV
- risk factors: immunosuppression, old age, occasionally associated with hematologic malignancy

### Differential Diagnosis
- before thoracic skin lesions occur, must consider other causes of chest pain
- contact dermatitis, localized bacterial infection, zosteriform HSV (more pathogenic for the eyes than VZV)

### Investigations
- none required, but can do Tzanck test, direct fluorescence antibody test, or viral culture to rule out HSV

### Prevention
- routine vaccination in 50+ yr old with Shingrix® (recombinant zoster vaccine) preferred to in 60+ yr old with Zostavax® (live zoster vaccine)

### Management
- compress with normal saline, Burow's or betadine solution
- oral antivirals: famciclovir, valacyclovir, or acyclovir for 7 d; must initiate within 72 h to be of benefit
- analgesia: NSAIDs, acetaminophen for mild-moderate pain; opioids if severe
- post-herpetic neuralgia: TCAs, anticonvulsants (gabapentin, pregabalin)

## MOLLUSCUM CONTAGIOSUM



### Clinical Feature
- discrete dome-shaped and umbilicated pearly, white papules caused by DNA Pox virus (Molluscum contagiosum virus)
- common sites: eyelids, beard (likely spread by shaving), neck, axillae, trunk, perineum, buttocks

### Etiology
- virus is spread via direct contact, auto-inoculation, sexual contact
- common in children and sexually active young adults (giant molluscum and severe cases can be seen in the setting of HIV)
- virus is self-limited and can take 1-2 yr to resolve

### Investigations
- none required, however can biopsy to confirm diagnosis

### Management
- topical cantharidin (a vesicant)
- cryotherapy
- curettage
- topical retinoids
- Aldara® (imiquimod): immune modulator that produces a cytokine inflammation

## WARTS (VERRUCA VULGARIS) (HUMAN PAPILLOMAVIRUS INFECTIONS)



**Table 19. Different Manifestations of HPV Infection**

| | Definition and Clinical Features | Differential Diagnosis | Distribution | HPV Type |
|---|---|---|---|---|
| **Verruca Vulgaris** (Common Warts) | Hyperkeratotic, elevated discrete epithelial growths with papillated surface caused by HPV<br>Paring of surface reveals punctate, red-brown specks (thrombosed capillaries) | Molluscum contagiosum, seborrheic keratosis | Located at trauma sites: fingers, hands, knees of children and teens | At least 80 types are known |
| **Verruca Plantaris** (Plantar Warts) and **Verruca Palmaris** (Palmar Warts) | Hyperkeratotic, shiny, sharply marginated growths<br>Paring of surface reveals red-brown specks (capillaries), interruption of epidermal ridges | May need to scrape ("pare") lesions to differentiate wart from callus and corn | Located at pressure sites: metatarsal heads, heels, toes | Commonly HPV 1, 2, 4, 10 |
| **Verruca Planae** (Flat Warts) | Multiple discrete, skin coloured, flat topped papules grouped or in linear configuration<br>Common in children | Syringoma, seborrheic keratosis, molluscum contagiosum, lichen planus | Sites: face, dorsa of hands, shins, knees | Commonly HPV 3, 10 |
| **Condyloma Acuminata** (Genital Warts) | Skin-coloured pinhead papules to soft cauliflower like masses in clusters<br>Can be asymptomatic, lasting months to years<br>Highly contagious, transmitted sexually and non-sexually (e.g. Koebner phenomenon via scratching, shaving), and can spread without clinically apparent lesions<br>Investigations: acetowhitening (subclinical lesions seen with 5% acetic acid x 5 min and hand lens)<br>Complications: fairy-ring warts (satellite warts at periphery of treated area of original warts) | Condyloma lata (secondary syphilitic lesion, dark field strongly +ve), molluscum contagiosum | Sites: genitalia and perianal areas | Commonly HPV 6 and 11<br>HPV 16, 18, 31, 33 cause cervical dysplasia, SCC, and invasive cancer |

### Treatment for Warts
- first line therapies
  - salicylic acid preparations (patches, solutions, creams, ointments), cryotherapy, topical cantharidin (Cantharone®)
- second line therapies
  - topical imiquimod, topical 5-fluorouracil, topical tretinoin, podophyllotoxin
- third line therapies
  - curettage, cautery, surgery for non plantar warts, $CO_2$ laser, oral cimetidine (particularly children), intralesional bleomycin (plantar warts), trichloroacetic acid, diphencyprone
- other viruses associated with skin changes, such as measles, roseola, fifth disease, etc.
- see Pediatrics, *Pediatric Exanthems*, P53

## Yeast Infections

### CANDIDIASIS

### Etiology
- many species of Candida (70-80% of infections are from *Candida albicans*)
- opportunistic infection in those with predisposing factors (e.g. trauma, malnutrition, immunodeficiency)

### Candidal Paronychia
- clinical feature: painful red swelling of periungual skin
- management: topical agents not as effective; oral antifungals recommended

### Candidal Intertrigo
- clinical feature
  - macerated/eroded erythematous patches that may be covered with papules and pustules, located in intertriginous areas often under breast, groin, or interdigitally
  - peripheral "satellite" pustules
  - starts as non-infectious maceration from heat, moisture, and friction
- predisposing factors: obesity, DM, systemic antibiotics, immunosuppression, malignancy
- management: keep area dry, terbinafine, ciclopirox olamine, ketoconazole/clotrimazole cream bid until rash clears

Oral Terbinafine (Lamisil®) is not effective because it is not secreted by sweat glands

### PITYRIASIS (TINEA) VERSICOLOR

### Clinical Feature
- asymptomatic superficial fungal infection with brown/white scaling macules
- affected skin darker than surrounding skin in winter, lighter in summer (does not tan)
- common sites: upper chest and back

### Pathophysiology
- microbe produces azelaic acid → inflammatory reaction inhibiting melanin synthesis yielding variable pigmentation
- affinity for sebaceous glands; require fatty acids to survive

### Etiology
- *Pityrosporum ovale* (*Malassezia furfur*)
- also associated with folliculitis and seborrheic dermatitis
- predisposing factors: summer, tropical climates, excessive sweating, Cushing's syndrome, prolonged corticosteroid use

### Investigations
- clinical diagnosis but can perform microscopic examination, KOH prep of scales for hyphae and spores

### Management
- ketoconazole shampoo or cream daily
- topical terbinafine or ciclopirox olamine bid
- systemic fluconazole or itraconazole for 7 d if extensive

## Sexually Transmitted Infections

### SYPHILIS

### Clinical Feature
- characterized initially by a painless ulcer (chancre)
- following inoculation, systemic infection with secondary and tertiary stages

### Etiology
- *Treponema pallidum*
- transmitted sexually, congenitally, or rarely by transfusion

**Table 20. Stages of Syphilis**

| | Clinical Feature | Investigations | Management |
|---|---|---|---|
| **Primary Syphilis** | Single red, indurated, painless chancre, that develops into painless ulcer with raised border and scanty serous exudate<br>Chancre develops at site of inoculation after 3 wk of incubation and heals in 4-6 wk; chancre may also develop on lips or anus<br>Regional non-tender lymphadenopathy appears <1 wk after onset of chancre<br>DDx: chancroid (painful), HSV (multiple lesions) | CANNOT be based on Clinical Feature alone<br>VDRL negative – repeat weekly for 1 mo<br>FTA-ABS test has greater sensitivity and may detect disease earlier in course<br>Dark field examination – spirochete in chancre fluid or lymph node aspirate | Penicillin G, 2.4 million units IM, single dose |
| **Secondary Syphilis** | Presents 2-6 mo after primary infection (patient may not recall presence of primary chancre)<br>Associated with generalized lymphadenopathy, splenomegaly, headache, chills, fever, arthralgias, myalgias, malaise, photophobia<br>Lesions heal in 1-5 wk and may recur for 1 yr<br>3 types of lesions:<br>1. Macules and papules: flat top, scaling, non-pruritic, sharply defined, circular/annular rash (DDx: pityriasis rosea, tinea corporis, drug eruptions, lichen planus)<br>2. Condyloma lata: wart-like moist papules around genital/perianal region<br>3. Mucous patches: macerated patches mainly found in oral mucosa | VDRL positive<br>FTA-ABS +ve; –ve after 1 yr following appearance of chancre<br>Dark field +ve in all secondary | As for primary syphilis |
| **Tertiary Syphilis** | Extremely rare<br>3-7 yr after secondary<br>Main skin lesion: 'Gumma' – a granulomatous non-tender nodule | As in primary syphilis, VDRL can be falsely negative | Penicillin G, 2.4 million units IM weekly x 3 wk |

**Natural History of Untreated Syphilis**
- Inoculation
- Primary syphilis (10-90 d after infection)
- Secondary syphilis (simultaneous to primary syphilis or up to 6 mo after healing of primary lesion)
- Latent syphilis
- Tertiary syphilis (2-20 yr)

**Latent Syphilis**
70% of untreated patients will remain in this stage for the rest of their lives and are immune to new primary infection

## GONOCOCCEMIA

### Clinical Feature
- disseminated gonococcal infection
- hemorrhagic, tender, pustules on a purpuric/petechial background
- common sites: distal aspects of extremities
- associated with fever, arthritis, urethritis, proctitis, pharyngitis, and tenosynovitis
- neonatal conjunctivitis if infected via birth canal

### Etiology
- *Neisseria gonorrhoeae*

### Investigations
- requires high index of clinical suspicion because tests are often negative
- bacterial culture of blood, joint fluid, and skin lesions
- joint fluid cell count and Gram stain

### Management
- notify Public Health authorities
- screen for other STIs
- cefixime 400 mg PO (drug of choice) or ceftriaxone 1 g IM

## HSV
- see *Viral Infections*, D29

## HPV
- see *Viral Infections*, D29

# Pre-Malignant Skin Conditions

## Actinic Keratosis (Solar Keratosis)

### Clinical Feature
- ill-defined, scaly, erythematous papules or plaques on a background of sun-damaged skin (solar heliosis)
- sandpaper-like, gritty sensation felt on palpation, often easier to appreciate on palpation rather than inspection
- sites: areas of sun exposure (face, ears, scalp if bald, neck, sun-exposed limbs)

**Types of AK**
- Erythematous: typical AK lesion
- Hypertrophic: thicker, rough papule/plaque
- Cutaneous horn: firm hyperkeratotic outgrowth
- Actinic cheilitis: confluent AKs on the lip
- Pigmented: flat, tan-brown, scaly plaque
- Spreading pigmented
- Proliferative
- Conjunctival: pinguecula, pterygium

### Pathophysiology
- UV radiation damage to keratinocytes from repeated sun exposure (especially UVB)
- risk of transformation of AK to SCC (~1/1000), but higher likelihood if AK is persistent
- UV-induced p53 gene mutation
- risk factors: increased age, light skin/eyes/hair, immunosuppression, syndromes such as albinism or xeroderma pigmenotsum
- risk factors for malignancy: immunosuppression, history of skin cancer, persistence of the AK

### Epidemiology
- common with increasing age, outdoor occupation, M>F
- skin phototypes I-III, rare in darker skin as melanin is protective

### Differential Diagnosis
- SCC in situ, superficial BCC, seborrheic keratosis, cutaneous lupus erythematosus

### Investigations
- biopsy lesions that are refractory to treatment

### Management
- destructive: cryotherapy, electrodessication, and curettage
- topical pharmacotherapy (mechanism: destruction of rapidly growing cells or immune system modulation)
  - topical 5-fluorouracil cream (for 2-4 wk), imiquimod 5% (2x/wk for 16 wk), imiquimod 3.75% (daily for 2 wk then none for 2 wk then daily for 2 wk), ingenol Mmbutate gel 0.015% (daily for 3 d on the head and neck), ingenol mebutate 0.05% gel (daily for 2 d on the body)
- photodynamic therapy
- excision

## Leukoplakia

### Clinical Feature
- a morphologic term describing homogeneous or speckled white plaques with sharply demarcated borders
- sites: oropharynx, most often floor of the mouth, soft palate, and ventral/lateral surfaces of the tongue

### Pathophysiology
- precancerous or premalignant condition
- oral form is strongly associated with tobacco use and alcohol consumption

### Epidemiology
- 1-5% prevalence in adult population after 30 yr of age; peak at age 50
- M>F, fair-skinned
- most common oral mucosal premalignant lesion

### Differential Diagnosis
- lichen planus, oral hairy leukoplakia, white sponge nevus

### Investigations
- biopsy is mandatory due to risk of malignancy

### Management
- low risk sites on buccal/labial mucosal or hard palate: eliminate carcinogenic habits, smoking cessation, follow-up
- moderate/dysplastic lesions: excision, cryotherapy

# Malignant Skin Tumours

## Non-Melanoma Skin Cancers

### BASAL CELL CARCINOMA

#### Subtypes
- noduloulcerative (typical)
  - skin-coloured papule/nodule with rolled, translucent ("pearly") telangiectatic border, and depressed/eroded/ulcerated centre
- pigmented variant
  - flecks of pigment in translucent lesion with surface telangiectasia
  - may mimic malignant melanoma
- superficial variant
  - flat, tan to red-brown plaque, often with scaly, pearly border, and fine telangiectasia at margin
  - least aggressive subtype
- sclerosing (morpheaform) variant
  - flesh/yellowish-coloured, shiny papule/plaque with indistinct borders, indurated

#### Pathophysiology
- malignant proliferation of basal keratinocytes of the epidermis
  - low grade cutaneous malignancy, locally aggressive (primarily tangential growth), rarely metastatic
  - usually due to UVB light exposure, therefore >80% on face
  - may also occur in previous scars, radiation, trauma, arsenic exposure, or genetic predisposition (Gorlin Syndrome)

#### Epidemiology
- most common malignancy in humans
- 75% of all malignant skin tumours >40 yr, increased prevalence in the elderly
- M>F, skin phototypes I and II, chronic cumulative sun exposure, ionizing radiation, immunosuppression, arsenic exposure

#### Differential Diagnosis
- benign: sebaceous hyperplasia, intradermal melanocytic nevus, dermatofibroma
- malignant: nodular malignant melanoma, SCC

#### Management
- imiquimod 5% cream (Aldara®) or cryotherapy is indicated for superficial BCCs on the trunk
- 5-fluorouracil and photodynamic therapy can also be used for superficial BCCs
- shave excision and electrodessication and curettage for most types of BCCs, not including morpheaform
- Mohs surgery: microscopically controlled, minimally invasive, stepwise excision for lesions on the face or in areas that are difficult to reconstruct
- radiotherapy used in advanced cases of BCC
- vismodegib is approved for metastatic BCC, also in syndromes characterized by multiple BCCs (Gorlin Syndrome)
- follow-up for new primary disease or recurrence
- 95% cure rate if lesion <2 cm in diameter or if treated early

**Workup/Investigations of BCC and Other NMSCs**
- **History**: duration, growth rate, family/personal Hx of skin cancer, prior therapy to the lesion
- **Physical**: location, size, whether circumscribed, tethering to deep structures, full skin exam, lymph node exam
- **Biopsy**: if shallow lesion, can do shave biopsy; otherwise punch or excisional biopsy may be more appropriate

**Surgical Margins**
- **Smaller lesions**: electrodessication and curettage with 2-3 mm margin of normal skin
- **Deep infiltrative lesions**: surgical excision with 3-5 mm margins beyond visible and palpable tumour border, which may require skin graft or flap; or Mohs surgery, which conserves tissue and does not require margin control

### BOWEN'S DISEASE (SQUAMOUS CELL CARCINOMA IN SITU)

#### Clinical Feature
- sharply demarcated erythematous patch/thin plaque with scale and/or crusting
- often 1-3 cm in diameter and found on the skin and mucous membranes
- evolves to SCC in 10-20% of cutaneous lesions and >20% of mucosal lesions

#### Management
- same as for BCC
- biopsy required for diagnosis
- topical 5-fluorouracil (Efudex®) or imiquimod (Aldara®) used if extensive and as a tool to identify margins of poorly defined tumours
- cryosurgery
- shave excision with electrodessication and curettage

## SQUAMOUS CELL CARCINOMA

### Clinical Feature
- hyperkeratotic indurated, pink/red/skin-coloured papule/plaque/nodule with surface scale/crust ± ulceration
- more rapid enlargement than BCC
- exophytic (grows outward), may present as a cutaneous horn
- sites: face, ears, scalp, forearms, dorsum of hands

### Pathophysiology
- malignant neoplasm of keratinocytes (primarily vertical growth)
- predisposing factors include: cumulative UV radiation, PUVA, ionizing radiation therapy/exposure, chemical carcinogens (such as arsenic, tar, and nitrogen mustards), HPV 16, 18, immunosuppression
- may occur in previous scar (SCC more commonly than BCC)

### Epidemiology
- second most common type of cutaneous neoplasm
- primarily on sun-exposed skin in the elderly, M>F, skin phototypes I and II, chronic sun exposure
- in organ transplant recipients, SCC is most common cutaneous malignancy, with increased mortality as compared to non-immunocompromised population

### Differential Diagnosis
- benign: nummular eczema, psoriasis, irritated seborrheic keratosis
- pre-malignant: Actinic Keratosis, Bowenoid papulosis
- malignant: keratoacanthoma, Bowen's disease, BCC, amelanotic melanoma

### Management
- surgical excision with primary closure, skin flaps or grafting
- Mohs surgery
- lifelong follow-up (more aggressive treatment than BCC)
- radiation therapy

### Prognosis
- good prognostic factors: early treatment, negative margins, and small size of lesion
- SCCs that arise from AK metastasize less frequently (~1%) than other SCCs arising *de novo* in old burns (2-5% of cases)
- overall control is 75% over 5 yr, rate of metastasis from primary SCC is 2-5%
- metastasis rates are higher if diameter >2 cm, depth >4 mm, recurrent, involvement of bone/muscle/nerve, location on scalp/ears/nose/lips, immunosuppressed, caused by arsenic ingestion, or tumour arose from scar/chronic ulcer/burn/genital tract/sinus tract

## KERATOACANTHOMA

### Clinical Feature
- rapidly growing, firm, dome-shaped, erythematous or skin-coloured nodule with central keratin-filled crater, resembling an erupting volcano
- may spontaneously regress within a year, leaving a scar
- sites: sun-exposed skin

### Pathophysiology
- epithelial neoplasm with atypical keratinocytes in epidermis
- low grade variant of SCC

### Etiology
- HPV, UV radiation, chemical carcinogens (tar, mineral oil)

### Epidemiology
- >50 yr, rare <20 yr

### Differential Diagnosis
- treat as SCC until proven otherwise
- nodular BCC, Merkel cell carcinoma, hypertrophic solar keratosis, verruca vulgaris

### Management
- surgical excision or saucerization (shave biopsy) followed by electrodesiccation of the base, treated similarly to SCC
- intralesional methotrexate injection





**Interventions for Actinic Keratosis**
Cochrane DB Syst Rev 2012;2:C004415
**Purpose**: To assess the efficacy of treatments for actinic keratosis.
**Methods**: Systematic review of RCTs.
**Results**: A total of 83 RCTs (10,036 patients) were included evaluating 24 treatments. Cryotherapy, diclofenac, 5-fluorouracil, imiquimod, ingenol mebutate, photodynamic therapy, resurfacing and trichloroacetic acid peel were all effective at treating actinic keratosis and generally comparable with one another. Skin irritation was more common with diclofenac and 5-fluorouracil. Photodynamic therapy and imiquimod treatment resulted in better cosmetic appearance.
**Conclusion**: For individual lesions, photodynamic therapy is more effective that cryotherapy. For field-directed treatments, 5-fluorouracil, diclofenac imiquimod and ingenol mebutate had comparable efficacy.

# Malignant Melanoma

## Clinical Feature
- malignant characteristics of a mole: "ABCDE" mnemonic
- sites: skin, mucous membranes, eyes, CNS
- ~2/3 arise de novo without an associated nevus

## Clinical Subtypes of Malignant Melanoma
- **lentigo maligna**
  - malignant melanoma *in situ* (normal and malignant melanocytes confined to the epidermis)
  - 2-6 cm, tan/brown/black uniformly flat macule or patch with irregular borders
  - lesion grows radially and produces complex colours
  - often seen in the elderly
  - 10% evolve to lentigo maligna melanoma
- **lentigo maligna melanoma** (15% of all melanomas)
  - older individuals, ~7th decade
  - malignant melanocytes invading into the dermis
  - associated with pre-existing solar lentigo, not pre-existing nevi
  - flat, brown, stain-like, gradually enlarging with loss of skin surface markings
  - with time, colour changes from uniform brown to dark brown with black and blue
  - found on all skin surfaces, especially those often exposed to sun, such as the face and hands
- **superficial spreading melanoma** (60-70% of all melanomas)
  - atypical melanocytes initially spread laterally in epidermis then invade the dermis
  - irregular, indurated, enlarging plaques with red/white/blue discolouration, focal papules or nodules
  - ulcerate and bleed with growth
  - subtype most likely associated with pre-existing nevus
- **nodular melanoma** (30% of all melanomas)
  - atypical melanocytes that initially grow vertically with little lateral spread
  - uniformly ulcerated, blue-black, and sharply delineated plaque or nodule
  - rapidly fatal
  - may be pink or have no colour at all, this is called an amelanotic melanoma
  - EFG = elevated, firm, growing
- **acral lentiginous melanoma** (5% of all melanomas)
  - ill-defined dark brown, blue-black macule
  - palmar, plantar, subungual skin
  - melanomas on mucous membranes have poor prognosis

## Pathophysiology
- malignant neoplasm of pigment-forming cells (melanocytes and nevus cells)

## Epidemiology
- incidence: 1/75 (Canada), 1/50 (US)
- risk factors: increasing age, fair skin, red hair, positive personal/family history, familial dysplastic nevus syndrome, 1 large congenital nevus (>20 cm), any dysplastic nevi, >50 common nevi, immunosuppression, sun exposure with sunburns, tanning beds
- most common sites: back (M), calves (F)
- worse prognosis if: male, on scalp, hands, feet, late lesion, no pre-existing nevus present

## Differential Diagnosis
- benign: nevi, solar lentigo, seborrheic keratosis
- malignant: pigmented BCC

## Management
- excisional biopsy preferable, otherwise incisional biopsy
- remove full depth of dermis and extend beyond edges of lesion only after histologic diagnosis
- beware of lesions that regress – tumour is usually deeper than anticipated
- high dose IFN for stage II (regional), chemotherapy (cis-platinum, BCG) and high dose IFN for stage III (distant) disease
- newer chemotherapeutic, gene therapies, and vaccines starting to be used in metastatic melanoma
- radiotherapy may be used as adjunctive treatment

**Table 21. American Joint Committee on Cancer Staging System Based on Breslow's Thickness of Invasion**

| Tumour Depth | Stage | Approximate 5 Yr Survival |
|---|---|---|
| T1 <1.0 mm | Stage I T1a – T2a | 5-yr survival 90% |
| T2 1.01-2.0 mm | Stage II T2b – T4b | 5-yr survival 70% |
| T3 2.01-4.0 mm | Stage III any nodes | 5-yr survival 45% |
| T4 >4.0 mm | Stage IV any mets | 5-yr survival 10% |

a = no ulceration; b = ulceration

**Does this Patient have a Mole or Melanoma?**

**ABCDE checklist**
**A**symmetry
**B**order (irregular and/or indistinct)
**C**olour (varied)
**D**iameter (increasing or >6 mm)
**E**nlargement, elevation, evolution (i.e. change in colour, size, or shape)

Sensitivity 92% (CI 82-96%)
Specificity 100% (CI 54-100%)

*JAMA* 1998;279:696-701

**Risk Factors for Melanoma**

**no SPF is a SIN**
**S**un exposure
**P**igment traits (blue eyes, fair/red hair, pale complexion)
**F**reckling
**S**kin reaction to sunlight (increased incidence of sunburn)
**I**mmunosuppressive states (e.g. renal transplantation)
**N**evi (dysplastic nevi; increased number of benign melanocytic nevi)

**Node Dissection for Lesions**
>1 mm thick OR <1 mm and ulcerated OR >1 mitoses/mm$^2$ (Stage IB or higher melanoma patients should be offered a sentinel lymph node biopsy)
- Assess sentinel node at time of wide excision

# Other Cutaneous Cancers

### CUTANEOUS T-CELL LYMPHOMA

#### Clinical Feature
- **Mycosis fungoides** (limited superficial type)
  - characterized by erythematous patches/plaques/nodules/tumours, which may be pruritic and poikilodermic (atrophy, telangiectasia, hyperpigmentation, hypopigmentation)
  - common sites include: trunk, buttocks, proximal limbs
  - mildly symptomatic, usually excellent prognosis for early disease
- **Sézary syndrome** (widespread systemic type)
  - rare variant characterized by erythroderma, lymphadenopathy, WBC >20 x $10^9$/L with Sézary cells
  - can be considered to have evolved from MF (not initially meeting diagnostic criteria), but more commonly arises *de novo*
  - associated with intense pruritus, alopecia, palmoplantar hyperkeratosis, and systemic symptoms (fatigue, fever)
  - often fatal

#### Pathophysiology
- clonal proliferation of skin-homing CD4 T-cells

#### Epidemiology
- >50 yr old, M:F 2:1

#### Differential Diagnosis
- tinea corporis, nummular dermatitis, psoriasis, DLE, Bowen's disease, adult T-Cell leukemia-lymphoma (ATL)

#### Investigations
- skin biopsy (histology, "lymphocyte antigen cell" markers, TcR gene arrangement)
- blood smear looking for Sézary cells or flow cytometry (e.g. CD4:CD8 >10 is Sézary)
- imaging (for systemic involvement)

#### Management
- **Mycosis fungoides**
  - depends on stage of disease
  - topical steroids and/or PUVA, NB-UVB (311-313 mm)
- **Sézary syndrome**
  - oral retinoids and IFN
  - extra-corporeal photopheresis
  - may need radiotherapy for total skin electron beam radiation
  - may maintain on UV therapy
  - other chemotherapy agents

# Diseases of Hair Density

## Hair Growth

- hair grows in a cyclic pattern that is defined in 3 stages (most scalp hairs are in anagen phase)
  1. growth stage = anagen phase
  2. transitional stage = catagen stage
  3. resting stage = telogen phase
- total duration of the growth stage reflects the type and location of hair: eyebrow, eyelash, and axillary hairs have a short growth stage in relation to the resting stage
- growth of the hair follicles is also based on the hormonal response to testosterone and DHT; this response is genetically controlled

**Hair Regrowth Potential**
Ability to regrow hair depends on location of inflammatory infiltrates on hair follicle as stem cells are located at the upper part (bulge region) of the hair follicle
- Scarring alopecia: Inflammatory infiltrates found in upper part of hair follicles, destroying stem cells
- Non-scarring alopecia: Hair follicle is not permanently damaged, and therefore spontaneous or treatment-induced regrowth is possible

## Non-Scarring (Non-Cicatricial) Alopecia

### ANDROGENETIC ALOPECIA

#### Clinical Feature
- male- or female-pattern alopecia
- males: fronto-temporal areas progressing to vertex, entire scalp may be bald
- females: widening of central part, "Christmas tree" pattern

#### Pathophysiology
- action of dihydrotestosterone (DHT) on hair follicles

#### Epidemiology
- males: early 20s-30s
- females: 40s-50s

**Hair Loss – TOP HAT**
**T**elogen effluvium, tinea capitis
**O**ut of Fe, Zn
**P**hysical: trichotillomania, "corn-row" braiding
**H**ormonal: hypothyroidism, androgenic
**A**utoimmune: SLE, alopecia areata
**T**oxins: heavy metals, anticoagulants, chemotherapy, vitamin A, SSRIs

### Management
- minoxidil (Rogaine®) solution or foam to reduce rate of loss/partial restoration
- females: spironolactone (anti-androgenic effects), cyproterone acetate (Diane-35®)
- males: finasteride (Propecia®) (5-α-reductase inhibitor) 1 mg/d
- hair transplant

## TELOGEN EFFLUVIUM

### Clinical Feature
- uniform decrease in hair density secondary to hairs leaving the growth (anagen) stage and entering the resting (telogen) stage of the cycle

### Pathophysiology
- variety of precipitating factors (i.e. post-partum, psychological stress, major illness)
- hair loss typically occurs 2-4 mo after exposure to precipitant
- regrowth occurs within a few months but may not be complete

## ANAGEN EFFLUVIUM

### Clinical Feature
- hair loss due to insult of hair follicle impairing its mitotic activity (growth stage)

### Pathophysiology
- precipitated by chemotherapeutic agents (most common), other meds (bismuth, levodopa, colchicine, cyclosporine), exposure to chemicals (thallium, boron, arsenic)
- dose-dependent effect
- hair loss 7-14 d after single pulse of chemotherapy; most clinically apparent after 1-2 mo
- reversible effect; follicles resume normal mitotic activity few weeks after agent stopped

## ALOPECIA AREATA

### Clinical Feature
- autoimmune disorder characterized by patches of complete hair loss often localized to scalp, but can affect eyebrows, beard, eyelashes, etc.
- may be associated with dystrophic nail changes – fine stippling, pitting
- "exclamation mark" pattern (hairs fractured and have tapered shafts, i.e. looks like "!")
- may be associated with pernicious anemia, vitiligo, thyroid disease, Addison's disease
- spontaneous regrowth may occur within months of first attack (worse prognosis if young at age of onset and extensive loss)
- frequent recurrence often precipitated by emotional distress
- alopecia totalis: complete loss of hair on scalp
- alopecia universalis: complete loss of scalp hair, eyelashes, eyebrows, and body hair

### Management
- excellent prognosis for localized disease
- topical corticosteroids and intralesional triamcinolone acetonide (corticosteroids) can be used for isolated patches
- systemic immunosuppressants for refractory or extensive disease
- immunomodulatory (diphencyprone, anthralin)

## OTHER
- trichotillomania: impulse-control disorder characterized by compulsive hair pulling with irregular patches of hair loss, and with remaining hairs broken at varying lengths
- traumatic (e.g. tight "corn-row" braiding of hair, wearing tight pony tails, tight tying of turbans)

# Scarring (Cicatricial) Alopecia

### Clinical Feature
- irreversible loss of hair follicles with fibrosis

### Etiology
- physical: radiation, burns
- infections: fungal, bacterial, TB, leprosy, viral (HSV)
- primary inflammatory – subdivided into lymphocytic, neutrophilic, and mixed
  - lymphocytic:
    - lichen planus (lichen planopilaris) – white scale around hair follicles, up to 50% have lichen planus at other body sites
    - DLE (note that SLE can cause an alopecia unrelated to DLE lesions which are non-scarring)
    - central centrifugal cicatricial alopecia (CCCA): seen in up to 40% of black women, starting at central scalp; one of most commonly diagnosed scarring alopecias, may be associated with hair care practices in this population



**DDx of Non-Scarring (Non-Cicatricial) Alopecia**
- **Autoimmune**
  - Alopecia areata
- **Endocrine**
  - Hypothyroidism
  - Androgens
- **Micronutrient deficiencies**
  - Iron
  - Zinc
- **Toxins**
  - Heavy metals
  - Anticoagulants
  - Chemotherapy
  - Vitamin A
- **Trauma to the hair follicle**
  - Trichotillomania
  - 'Corn-row' braiding
- **Other**
  - Syphilis
  - Severe illness
  - Childbirth



**Precipitants of Telogen Effluvium**
**"SEND"** hair follicles out of anagen and into telogen
**S**tress and **S**calp disease (surgery)
**E**ndocrine (hypothyroidism, post-partum)
**N**utritional (iron and protein deficiency)
**D**rugs (citretin, heparin, lithium, IFN, β-blockers, valproic acid, SSRIs)



**Non-scarring alopecia:** intact hair follicles on exam → biopsy not required (but may be helpful)
**Scarring alopecia:** absent hair follicles on exam → biopsy required



**Alopecia Areata Subtypes**

Alopecia totalis: loss of all scalp hair and eyebrows

Alopecia universalis: loss of all body hair

  - neutrophilic:
    - folliculitis decalvans – discharge of pus and blood, tufting of hair follicles
    - dissecting cellulitis of the scalp – follicular papules, pustutles, nodules, and abscesses develop on the scalp
  - mixed
    - acne keloidalis nuchae – Dome-shaped papules, pustules, and plaques on the occipital scalp
- morphea: "coup de sabre" with involvement of centre of scalp

### Investigations
- biopsy from active border

### Management
- infections: treat underlying infection
- inflammatory: topical/intralesional steroids, anti-inflammatory antibiotics, antimalarials

# Nails and Disorders of the Nail Apparatus



**Table 22. Nail Changes in Systemic and Dermatological Conditions**

| Nail Abnormality | Definition/Etiology | Associated Disease |
|---|---|---|
| **NAIL PLATE CHANGES** | | |
| **Clubbing** | Proximal nail plate has greater than 180° angle to nail fold, watch-glass nails, bulbous digits | Cyanotic heart disease, bacterial endocarditis, pulmonary disorders, GI disorders, etc. |
| **Koilonychia** | Spoon shaped nails | Fe deficiency, malnutrition, DM |
| **Onycholysis** | Separation of nail plate from nail bed | Psoriasis, dermatophytes, thyroid disease |
| **Onychogryphosis** | Hypertrophy of the nail plate producing a curved, claw-like deformity | Poor circulation, chronic inflammation, tinea |
| **Onychohemia** | Subungual hematoma | Trauma to nail bed |
| **Onychomycosis** | Fungal infection of nail (e.g. dermatophyte, yeast, mould) | HIV, DM, peripheral arterial disease |
| **Onychocryptosis** | Ingrown toenail often hallux with congenital malalignment, painful inflammation, granulation tissue | Tight fitting shoes, excessive nail clipping |
| **SURFACE CHANGES** | | |
| **V-Shaped Nicking** | Distal margin has v-shaped loss of the nail plate | Darier's disease (keratosis follicularis) |
| **Pterygium Inversus Unguium** | Distal nail plate does not separate from underlying nail bed | Scleroderma |
| **Pitting** | Punctate depressions that migrate distally with growth | Psoriasis (random pattern), alopecia areata (geometric, grid-shaped arrangement), eczema |
| **Transverse Ridging** | Transverse depressions often more in central portion of nail plate | Serious acute illness slows nail growth (when present in all nails = Beau's lines), eczema, chronic paronychia, trauma |
| **Transverse White Lines** | Bands of white discolouration | Poisons, hypoalbuminemia (Muehrcke's lines) |
| **COLOUR CHANGES** | | |
| **Yellow** | | Tinea, jaundice, tetracycline, pityriasis rubra pilaris, yellow nail syndrome, psoriasis, tobacco use |
| **Green** | | *Pseudomonas* |
| **Black** | | Melanoma, hematoma |
| **Brown** | | Nicotine use, psoriasis, poisons, longitudinal melanonychia (ethnic) |
| **Splinter Hemorrhages** | Extravasation of blood from longitudinal vessels of nail bed, blood attaches to overlying nail plate and moves distally as it grows | Trauma, bacterial endocarditis, blood dyscrasias, psoriasis |
| **Oil Spots** | Brown-yellow discolouration | Psoriasis |
| **NAIL FOLD CHANGES** | | |
| **Herpetic Whitlow** | HSV infection of distal phalanx | HSV infection |
| **Paronychia** | Local inflammation of the nail fold around the nail bed | Acute: painful infection<br>Chronic: constant wetting (e.g. dishwashing, thumbsucking) |
| **Nail Fold Telangiectasias** | Cuticular hemorrhages, roughness, capillary changes | Scleroderma, SLE, dermatomyositis |
| **LOSS OF NAILS** | | |
| **Temporary Loss** | Occurs without scarring | Trauma (especially toenails or fingernails after large subungal hematoma), Beau's lins after severe illness |
| **Permanent Loss** | Occurs with scarring | Lichen planus (pterygium), genetic abnormalities (rare) |

# Skin Manifestations of Systemic Disease



**Table 23. Skin Manifestations of Internal Conditions**

| Disease | Related Dermatoses |
|---|---|
| **AUTOIMMUNE DISORDERS** | |
| **Behçet's Disease** | Painful aphthous ulcers in oral cavity ± genital mucous membranes, erythema nodosum, acneiform papules |
| **Buerger's Disease** | Superficial migratory thrombophlebitis, pallor, cyanosis, gangrene, ulcerations, digital resorptions |
| **Dermatomyositis** | Periorbital and extensor violaceous erythema, heliotrope with edema, Gottron's papules (violaceous flat-topped papules with atrophy), periungual erythema, telangiectasia, calcinosis cutis |
| **Polyarteritis Nodosa** | Subcutaneous nodules, stellate purpura, erythema, gangrene, splinter hemorrhages, livedo reticularis, ulceration |
| **Reactive Arthritis** | Keratoderma blennorrhagica (on feet), balanitis circinata (on male penis) |
| **Rheumatic Fever** | Petechiae, urticaria, erythema nodosum, rheumatic nodules, evanescent rash |
| **Scleroderma** | Raynaud's, nonpitting edema, waxy/shiny/tense atrophic skin (morphea), ulcers, cutaneous calcification, periungual telangiectasia, acrosclerosis, salt-and-pepper pigmentation |
| **SLE** | Malar erythema, discoid rash (erythematous papules or plaques with keratotic scale, follicular plugging, atrophic scarring on face, hands, and arms), hemorrhagic bullae, palpable purpura, urticarial purpura, patchy/diffuse alopecia, mucosal ulcers, photosensitivity |
| **Crohn's Disease/UC** | Pyoderma gangrenosum, erythema nodosum, Sweet's syndrome |
| **ENDOCRINE DISORDERS** | |
| **Addison's Disease** | Generalized hyperpigmentation or limited to skin folds, buccal mucosa, and scars |
| **Cushing's Syndrome** | Moon facies, purple striae, acne, hyperpigmentation, hirsutism, atrophic skin with telangiectasia |
| **Diabetes Mellitus** | Infections (e.g. boils, carbuncles, candidiasis, *S. aureus*, dermatophytoses, tinea pedis and cruris, infectious eczematoid dermatitis), pruritus, eruptive xanthomas, necrobiosis lipoidica diabeticorum, granuloma annulare, diabetic foot, diabetic bullae, acanthosis nigricans, calciphylaxis |
| **Hyperthyroidism** | Moist, warm skin, seborrhea, acne, nail atrophy, hyperpigmentation, toxic alopecia, pretibial myxedema, acropachy, onycholysis |
| **Hypothyroidism** | Cool, dry, scaly, thickened, hyperpigmented skin; toxic alopecia with dry, coarse hair, brittle nails, myxedema, loss of lateral 1/3 eyebrows |
| **HIV-RELATED** | |
| **Infections** | Viral (e.g. HSV, HZV, HPV, CMV, *Molluscum contagiosum*, oral hairy leukoplakia), bacterial (impetigo, acneiform folliculitis, dental caries, cellulitis, bacillary epithelioid angiomatosis, syphilis), fungal (candidiasis, histoplasmosis, cryptococcus, blastomycosis) |
| **Inflammatory Dermatoses** | Seborrhea, psoriasis, pityriasis rosea, vasculitis |
| **Malignancies** | Kaposi's sarcoma, lymphoma, BCC, SCC, MM |
| **MALIGNANCY** | |
| **Adenocarcinoma** | |
| Gastrointestinal | Peutz-Jeghers: pigmented macules on lips/oral mucosa |
| Cervix/anus/rectum | Paget's disease: eroding scaling plaques of perineum |
| **Carcinoma** | |
| Breast | Paget's disease, eczematous and crusting lesions of the skin of the nipple and usually areola of the breast |
| GI | Palmoplantar keratoderma: thickened skin of palms/soles |
| Thyroid | Sipple's syndrome: multiple mucosal neuromas |
| Breast/lung/ovary | Dermatomyositis: heliotrope erythema of eyelids and violaceous plaques over knuckles |
| **Lymphoma/Leukemia** | |
| Hodgkin's | Ataxia Telangiectasia: telangiectasia on pinna, bulbar conjunctiva |
| Acute leukemia | Ichthyosis: generalized scaling especially on extremities, Sweet's syndrome<br>Bloom's syndrome: butterfly erythema on face, associated with short stature |
| **Multiple Myeloma** | Amyloidosis: large, smooth tongue with waxy papules on eyelids, nasolabial folds and lips, as well as facial petechiae |
| **OTHERS** | |
| **Liver Disease** | Pruritus, hyperpigmentation, spider nevi, palmar erythema, white nails (Terry's nails), porphyria cutanea tarda, xanthomas, hair loss, jaundice |
| **Renal Disease** | Pruritus, pigmentation, half and half nails, perforating dermatosis, calciphylaxis |
| **Pruritic Urticarial Papules and Plaques of Pregnancy** | Erythematous papules or urticarial plaques in distribution of striae distensae: buttocks, thighs, upper inner arms, and lower back |
| **Cryoglobulinemia** | Palpable purpura in cold-exposed areas, Raynaud's, cold urticaria, acral hemorrhagic necrosis, bleeding disorders, associated with hepatitis C infection |



**Raynaud's Phenomenon DDx**

**COLD HAND**
**C**ryoglobulins/**C**ryofibrinogens
**O**bstruction/**O**ccupational
**L**upus erythematosus, other connective tissue disease
**D**M/**D**rugs
**H**ematologic problems (polycythemia, leukemia, etc.)
**A**rterial problems (atherosclerosis)
**N**eurologic problems (vascular tone)
**D**isease of unknown origin (idiopathic)



**Acanthosis Nigricans**
An asymptomatic dark thickened velvety hyperpigmentation of flexural skin most commonly around the neck. Associated with DM, obesity, and other endocrine disorders, and malignancy. It is a cutaneous marker of tissue insulin resistance

# Pediatric Exanthems

• see Pediatrics, P53

# Miscellaneous Lesions

## Angioedema and Urticaria

### Angioedema

- deeper swelling of the skin involving subcutaneous tissues; often involves the eyes, lips, and tongue
- may or may not accompany urticaria
- hereditary or acquired forms
- hereditary angioedema (does not occur with urticaria)
  - onset in childhood; 80% have positive family history
  - recurrent attacks; 25% die from laryngeal edema
  - triggers: minor trauma, emotional upset, temperature changes
- types of acquired angioedema
  - acute allergic angioedema (allergens include food, drugs, contrast media, insect venom, latex)
  - non-allergic drug reaction (drugs include ACEI)
  - acquired C1 inhibitor deficiency
- treatment
  - prophylaxis with danazol or stanozolol for hereditary angioedema
  - epinephrine pen to temporize until patient reaches hospital in acute attack

### Urticaria

- also known as "hives"
- transient, red, pruritic well-demarcated wheals
- each individual lesion lasts less than 24 h
- second most common type of drug reaction
- results from release of histamine from mast cells in dermis
- can also result after physical contact with allergen

**Table 24. Classification of Urticaria**

| Type | Etiology |
|---|---|
| **Acute Urticaria**<br>>2/3 of cases<br>Attacks last <6 wk<br>Individual lesions last <24 h | Drugs: especially ASA, NSAIDs<br>Foods: nuts, shellfish, eggs, fruit<br>**Idiopathic**<br>Infection<br>Insect stings (bees, wasps, hornets)<br>Percutaneous absorption: cosmetics, work exposures<br>Stress<br>Systemic diseases: SLE, endocrinopathy, neoplasm |
| **Chronic Urticaria**<br><1/3 of cases<br>Attacks last >6 wk<br>Individual lesion lasts <24 h | IgE-dependent: trigger associated<br>**Idiopathic (90% of chronic urticaria patients)**<br>Aeroallergens<br>Drugs (antibiotics, hormones, local anesthetics)<br>Foods and additives<br>Insect stings<br>Parasitic infections<br>Physical contact (animal saliva, plant resins, latex, metals, lotions, soap)<br>Direct mast cell release<br>Opiates, muscle relaxants, radio-contrast agents<br>Complement-mediated<br>Serum sickness, transfusion reactions<br>Infections, viral/bacterial (>80% of urticaria in pediatric patients)<br>Urticarial vasculitis<br>Arachidonic acid metabolism<br>ASA, NSAIDs<br>Physical<br>Dermatographism (friction, rubbing skin), cold (ice cube, cold water), cholinergic (hot shower, exercise), solar, pressure (shoulder strap, buttocks), aquagenic (exposure to water), adrenergic (stress), heat<br>Other<br>Mastocytosis, urticaria pigmentosa |
| **Urticarial Vasculitis**<br>Individual lesions last >24 h<br>Often painful, less likely pruritic, heals with bruise type lesions<br>Requires biopsy | Idiopathic<br>Infections<br>Hepatitis<br>Autoimmune diseases<br>SLE<br>Drug hypersensitivity<br>Cimetidine and diltiazem |

**DDx for Urticaria**

**DAM HIVES**
**D**rugs and foods
**A**llergic
**M**alignancy
**H**ereditary
**I**nfection
**V**asculitis
**E**motions
**S**tings

**Approach to Urticaria**

- Thorough Hx and P/E
- **Acute:** no immediate investigations needed; consider referral for allergy testing
- **Chronic:** further investigations required: CBC and differential, urinalysis, ESR, TSH, LFTs to help identify underlying cause
- **Vasculitic:** biopsy of lesion and referral to dermatology

**Wheal**

- Typically erythematous flat-topped, palpable lesions varying in size with circumscribed dermal edema
- Individual lesion lasts <24 h
- Associated with mast cell release of histamine
- May be pruritic

**Mastocytosis (Urticaria Pigmentosa)**

Rare disease due to excessive infiltration of the skin by mast cells. It manifests as many reddish-brown elevated plaques and macules. Friction to a lesion produces a wheal surrounded by intense erythema (Darier's sign), due to mast cell degranulation; this occurs within minutes

# Erythema Nodosum



### Clinical Feature
- acute or chronic inflammation of subcutaneous fat (panniculitis)
- round, red, tender, poorly demarcated nodules
- sites: asymmetrically arranged on extensor lower legs (typically shins), knees, arms
- associated with arthralgia, fever, malaise

### Etiology
- 40% are idiopathic
- drugs: sulfonamides, OCPs (also pregnancy), analgesics, trans retinoic acid
- infections: GAS, TB, histoplasmosis, *Yersinia*
- inflammation: sarcoidosis, Crohn's > UC
- malignancy: acute leukemia, Hodgkin's lymphoma

### Epidemiology
- 15-30 yr old, F:M 3:1
- lesions last for days and spontaneously resolve in 6 wk

### Investigations
- CXR (to rule out chest infection and sarcoidosis)
- throat culture, ASO titre, PPD skin test

### Management
- symptomatic: bed rest, compressive bandages, wet dressings
- NSAIDs, intralesional steroids
- treat underlying cause



**DDx of Erythema Nodosum**

**NODOSUMM**
**NO** cause (idiopathic) in 40%
**D**rugs (sulfonamides, OCP, etc.)
**O**ther infections (GAS+)
**S**arcoidosis
**UC** and Crohn's
**M**alignancy (leukemia, Hodgkin's lymphoma)
**M**any Infections

# Pruritus



### Clinical Feature
- a sensation provoking a desire to scratch, with or without skin lesions
- lesions may arise from the underlying disease, or from excoriation causing crusts, lichenified plaques, or wheals



**DDx of Pruritus**

**SCRATCHED**
**S**cabies
**C**holestasis
**R**enal
**A**utoimmune
**T**umours
**C**razies (psychiatric)
**H**ematology (polycythemia, lymphoma)
**E**ndocrine (thyroid, parathyroid, Fe)
**D**rugs, Dry skin

### Etiology
- dermatologic – generalized
  - asteatotic dermatitis ("winter itch" due to dry skin)
  - pruritus of senescent skin (may not have dry skin, any time of year)
  - infestations: scabies, lice
  - drug eruptions: ASA, antidepressants, opiates
  - psychogenic states
- dermatologic – local
  - atopic and contact dermatitis, lichen planus, urticaria, insect bites, dermatitis herpetiformis
  - infection: varicella, candidiasis
  - lichen simplex chronicus
  - prurigo nodularis
- systemic disease – usually generalized
  - hepatic: obstructive biliary disease, cholestatic liver disease of pregnancy
  - renal: chronic renal failure, uremia secondary to hemodialysis
  - hematologic: Hodgkin's lymphoma, multiple myeloma, leukemia, polycythemia vera, hemochromatosis, Fe deficiency anemia, cutaneous T-cell lymphoma
  - neoplastic: lung, breast, gastric (internal solid tumours), non-Hodgkin's lymphoma
  - endocrine: carcinoid, DM, hypothyroid/thyrotoxicosis
  - infectious: HIV, trichinosis, echinococcosis, hepatitis C
  - psychiatric: depression, psychosis
  - neurologic: post-herpetic neuralgia, multiple sclerosis



Consider biopsy of any nonhealing wound to rule out cancer

### Investigations
- blood work: CBC, ESR, Cr/BUN, LFT, TSH, fasting blood sugar, stool culture, and serology for parasites

### Management
- treat underlying cause
- cool water compresses to relieve pruritus
- bath oil and emollient ointment (especially if xerosis is present)
- topical corticosteroid and antipruritics (e.g. menthol, camphor, phenol, mirtazapine, capsaicin)
- systemic antihistamines: H1 blockers are most effective, most useful for urticaria
- phototherapy with UVB or PUVA
- doxepin, amitriptyline
- immunosuppressive agents if severe: steroids and steroid-sparing

# Wounds and Ulcers

- see Plastic Surgery, PL8, PL16

# Sunscreens and Preventative Therapy

## Sunburn (Solar Erythema)

- erythema 2-6 h post UV exposure often associated with edema, pain and blistering with subsequent desquamation of the dermis, and hyperpigmentation
- chronic UVA and UVB exposure leads to photoaging, immunosuppression, photocarcinogenesis
- prevention: avoid peak UVR (10 am-4 pm), wear appropriate clothing, wide-brimmed hat, sunglasses, and broad-spectrum sunscreen
- clothing with UV protection expressed as UV protection factor (UPF) is analogous to SPF of sunscreen

## Sunscreens

- under ideal conditions an SPF of 10 means that a person who normally burns in 20 min will burn in 200 min following the application of the sunscreen
- topical chemical: absorbs UV light
  - requires application at least 15-30 min prior to exposure, should be reapplied every 2 h (more often if sweating, swimming)
  - UVB absorbers: PABA, salicylates, cinnamates, benzylidene camphor derivatives
  - UVA absorbers: benzophenones, anthranilates, dibenzoylmethanes, benzylidene camphor derivatives
- topical physical: reflects and scatters UV light
  - titanium dioxide, zinc oxide, kaolin, talc, ferric chloride, and melanin
  - all are effective against the UVA and UVB spectrum
  - less risk of sensitization than chemical sunscreens and waterproof, but may cause folliculitis or miliaria
- some sunscreen ingredients may cause contact or photocontact allergic reactions, but are uncommon

## Management

- sunburn: if significant blistering present, consider treatment in hospital; otherwise, symptomatic treatment (cool wet compresses, oral anti-inflammatory, topical corticosteroids)
- antioxidants, both oral and topical are being studied for their abilities to protect the skin; topical agents are limited by their ability to penetrate the skin

# Topical Steroids

**Table 25. Potency Ranking of Topical Steroids**

| Relative Potency | Relative Strength | Generic Names | Trade Names | Usage |
|---|---|---|---|---|
| **Weak** | x1 | hydrocortisone – 2.5% (1% available over-the-counter) | Emo Cort® | Intertriginous areas, children, face, thin skin |
| **Moderate** | x3 | hydrocortisone 17-valerate – 0.2%<br>desonide<br>mometasone furoate | Westcort®<br>Tridesilon®<br>Elocom® | Arm, leg, trunk |
| **Potent** | x6 | betamethasone – 0.1% 17-valerate – 0.1% amcinonide | Betnovate®<br>Celestoderm – V®<br>Cyclocort® | Body |
| **Very Potent** | x9 | betamethasone dipropionate – 0.05%<br>fluocinonide – 0.05%<br>halcinonide | Diprosone®<br>Lidex, Topsyn gel®<br>Lyderm®<br>Halog® | Palms and soles |
| **Extremely Potent** | x12 | clobetasol propionate – 0.05% (most potent)<br>betamethasone dipropionate ointment<br>halobetasol propionate – 0.05% | Dermovate®<br>Diprolene®<br>Ultravate® | Palms and soles |

**Skin Phototypes (Fitzpatrick)**

| Phototype | Colour of Skin | Skin's Response to Sun Exposure (without SPF protection) |
|---|---|---|
| I | White | Always burns, never tans |
| II | White | Always burns, little tan |
| III | White | Slight burn, slow tan |
| IV | Pale brown | Slight burn, faster tan |
| V | Brown | Rarely burns, dark tan |
| VI | Dark brown or black | Never burns, dark tan |

**SPF** = burn time with cream/burn time without cream

**UV Radiation**

**UVA (320-400 nm): Aging**
- Penetrates skin more effectively than UVB or UVC
- Responsible for tanning, burning, wrinkling, photoallergy, and premature skin aging
- Penetrates clouds, glass and is reflected off water, snow, and cement

**UVB (290-320 nm): Burning**
- Absorbed by the outer dermis
- Is mainly responsible for burning and premature skin aging
- Primarily responsible for BCC, SCC
- Does not penetrate glass and is substantially absorbed by ozone

**UVC (200-290 nm)**
- Is filtered by ozone layer

**Body Site: Relative Percutaneous Absorption**

| | |
|---|---|
| Forearm | 1.0 |
| Plantar foot | 0.14 |
| Palm | 0.83 |
| Back | 1.7 |
| Scalp | 3.7 |
| Forehead | 6.0 |
| Cheeks | 13.0 |
| Scrotum | 42.0 |

Calculation of strength of steroid compared to hydrocortisone on forearm: relative strength of steroid x relative percutaneous absorption

**Side Effects of Topical Steroids**
- Local: atrophy, perioral dermatitis, steroid acne, rosacea, contact dermatitis, tachyphylaxis (tolerance), telangectasis, striae, hypertrichosis, hypopigmentation
- Systemic: suppression of HPA axis

# Dermatologic Therapies

## Table 26. Common Topical Therapies

| Drug Name | Dosing Schedule | Indications | Comments |
|---|---|---|---|
| **Calcipotriol** (Dovonex®) | 0.005% cream, ointment, scalp solution, apply bid<br>For maintenance therapy apply OD | Psoriasis | Burning, itching, skin irritation, worsening of psoriasis<br>Avoid face, mucous membranes, eyes; wash hands after application<br>Maximum weekly dosage of cream by age:<br>2-5 yr – 25 g/wk<br>6-10 yr – 50 g/wk<br>11-14 yr – 75 g/wk<br>>14 yr – 100 g/wk<br>Inactivated by light (do not apply before phototherapy) |
| **Imiquimod** (Aldara®) | 5% cream applied 3x/wk<br>Apply at bedtime, leave on 6-10 h, then wash off with mild soap and water<br>Max duration 16 wk | Genital warts<br>Cutaneous warts<br>AK<br>Superficial BCC | Avoid natural/artificial UV exposure<br>Local skin and application site reactions<br>Erythema, ulceration, edema, flu-like symptoms<br>Works best for warts on mucosal surfaces<br>May induce inflammation and erosion |
| **Permethrin** (Kwellada® P Lotion and Nix® Dermal Cream) | 1% or 5% cream, applied once overnight to all skin areas from neck down, repeated one week later | Scabies (Kwellada-P Lotion, Nix® Dermal Cream)<br>Pediculosis (Kwellada-P Crème Rinse®, Nix Crème Rinse®) | Do not use in children <2 yr<br>Hypersensitivity to drug, or known sensitivity to chrysanthemums<br>Local reactions only (resolve rapidly); including burning, pruritus<br>Low toxicity, excellent results<br>Consider second application after 7 d |
| **Pimecrolimus** (Elidel®) | 1% cream bid<br>Use for as long as lesions persist and discontinue upon resolution of symptoms | AD (mild to moderate) | Burning<br>Lacks adverse effects of steroids<br>May be used on all skin surfaces including head, neck, and intertriginous areas<br>Expensive |
| **Tacrolimus Topical** (Protopic®) | 0.03% (children) or 0.1% (adults) ointment bid<br>Continue for duration of disease PLUS 1 wk after clearing | AD (mild to moderate) | Burning<br>Lacks adverse effects of steroids<br>May be used on all skin surfaces including head, neck, and intertriginous areas<br>Expensive |

**Topical Vehicles**
- **Ointment** (water in oil): hydrate, greasy
- **Cream** (oil in water): hydrate, variable
- **Lotion** (powder in water): drying, cosmesis
- **Solutions** (water, alcohol, propylene glycol)
- **Gel** (solution that melts on contact with skin, alcohol): drying
- **Foam** is a newer vehicle and several agents are now available in foam vehicles. Examples include Olux-E (clobetasol), Verdesso (desonide), Luxiq (betamethasone), and Enstilar (betamethasone propionate and calcipotriol)
- **Sprays**: Lamisil (terbinafine) spray, Clobex spray (clobetasol)
- **Laquers**: Penlac (ciclopirox), Jublia (efinaconazole)

**Deciding on the Amount of Steroid to Use**
- 1 palm = 1% BSA
- 1 fingertip unit (FTU) = Amount of topical medication (from 5 mm nozzle) placed on pad of index finger from distal tip to DIP = 500 mg = 2% BSA
- Therefore give 30 g for every 2 palms of area to cover (if applying steroid BID, 1 mo supply)

## Table 27. Common Oral Therapies

| Drug Name | Dosing Schedule | Indications | Comments |
|---|---|---|---|
| **Acitretin** (Soriatane®) | 25-50 mg PO OD; maximum 75 mg/d | Severe psoriasis<br>Other disorders of hyperkeratinization (ichthyosis, Darier's disease) | Monitoring strategies<br>Monitor lipids, LFTs at baseline and q1-2wk until stable<br>Contraindications<br>Women of childbearing potential unless strict contraceptive requirements are met<br>Drug interactions<br>Other systemic retinoids, methotrexate, tetracyclines, certain contraceptives<br>May be combined with PUVA phototherapy (known as re-PUVA) |
| **Antivirals** | famciclovir (Famvir®)<br>250 mg PO tid x 7-10 d (for 1st episode of genital herpes)<br>125 mg PO bid x 5 d (for recurrent genital herpes) | Chickenpox<br>Herpes zoster<br>Genital herpes<br>Acute and prophylactic to reduce transmission in infected patients<br>Herpes labialis | Side effects<br>Headache, nausea, diarrhea, abdominal pain<br>Reduce dose if impaired renal function |
| | valacyclovir (Valtrex®)<br>1000 mg PO bid x 7-10 d<br>(for 1st episode of genital herpes)<br>500 mg PO bid x 5 d<br>(for recurrent genital herpes) | | Side effects<br>Dizziness, depression, abdominal pain<br>Reduce dose if impaired renal function<br>Drug interactions<br>cimetidine |
| **Cyclosporine** (Neoral®) | 2.5-4 mg/kg/d PO divided bid<br>Max 4 mg/kg/d<br>After 4 wk may increase by 0.5 mg/kg/d q2wk<br>Concomitant dose of magnesium may protect the kidneys | Psoriasis<br>May also be effective in:<br>Lichen planus<br>EM<br>Recalcitrant urticaria<br>Recalcitrant AD | Monitoring strategies<br>Blood pressure, renal function<br>Contraindications<br>Abnormal renal function, uncontrolled hypertension, malignancy (except NMSC), uncontrolled infection, immunodeficiency (excluding autoimmune disease), hypersensitivity to drug<br>Long-term effects preclude use of cyclosporine for >2 yr; discontinue earlier if possible<br>May consider rotating therapy with other drugs to minimize adverse effects of each drug |
| **Dapsone** | 50-100-150 mg PO OD tapering to 25-50 mg PO OD to as low as 50 mg 2x/wk | Dermatitis herpetiformis, neutrophilic dermatoses | Monitoring strategies<br>Obtain G6PD levels before initiating; in the initial 2 wk obtain methemoglobin levels and follow the blood counts carefully for the first few months<br>Side effects<br>Neuropathy<br>Hemolysis (Vitamin C and E supplementation can help prevent this)<br>Drug interactions<br>Substrate of CYP2C8/9 (minor), 2C19 (minor), 2E1 (minor), 3A4 (major)<br>Often a dramatic response within hours |

**Table 27. Common Oral Therapies** (continued)

| Drug Name | Dosing Schedule | Indications | Comments |
|---|---|---|---|
| **Doxycycline** | 50 mg PO bid | Acne vulgaris<br>Rosacea<br>Bullous pemphigoid | Contraindications<br>Pregnancy, hepatic impairment, drug hypersensitivity<br>Taking acitretin, isotretinoin, or penicillin antibiotic<br>Oral typhoid vaccine |
| **Isotretinoin** (Accutane®) | 0.5-1 mg/kg/d given OD to achieve a total dose of 120 mg/kg (20-24 wk) | Severe nodular and/or inflammatory acne<br>Acne conglobata<br>Recalcitrant acne<br>Widespread comedonal acne | Monitoring strategies<br>Baseline lipid profile and LFTs before treatment, β-hCG<br>Contraindications<br>Teratogenic – in sexually active females, 2 forms of reliable contraception necessary<br>Generally regarded as unsafe in lactation<br>Side effects<br>Decreased night vision, decreased tolerance to contact lenses, dry mucous membranes<br>May transiently exacerbate acne, dry skin<br>Depression, myalgia<br>Drug interactions<br>Caution if used at the same time as tetracyclinefamily antibiotics – both may cause pseudotumour cerebri<br>Discontinue vitamin A supplements<br>Drug may be discontinued at 16-20 wk when nodule count has dropped by >70%; a second course may be initiated after 2 mo prn<br>Refractory cases may require >3 courses |
| **Itraconazole** (Sporanox®) | 100-400 mg PO OD, depending on infection<br>Tinea corporis/cruris/versicolor: 200 mg PO OD x 7 d<br>Tinea pedis: 200 mg PO bid x 7 d<br>Toenails: 200 mg PO bid x 7 d once per month, repeated 3x<br>Fingernail involvement only: 200 mg bid PO x 7 d once per month, repeated 2x | Onychomycosis<br>Tinea corporis, cruris, pedis, versicolor, capitis | Contraindications<br>CHF<br>Side effects<br>Serious hepatotoxicity<br>Drug Interactions<br>Inhibits CYP3A4<br>Increases concentration of some drugs metabolized by this enzyme (i.e. statins, diabetic drugs)<br>Give capsules with food, capsules must be swallowed whole |
| **Ivermectin** (Mectizan®, Stromectol®) | 200-250 µg/kg PO qweekly x 2<br>Take once as directed; repeat one wk later | Onchocerciasis (USA only)<br>Not licensed for use in Canada<br>Also effective for: scabies | No significant serious side effects<br>Efficacious |
| **Methotrexate** | 10-25 mg qwk, PO, IM, or IV<br>Max: 30 mg/wk<br>To minimize side effects, administer with folic acid supplementation:<br>1-5 mg OD | Psoriasis<br>AD<br>Lymphomatoid papulosis<br>May also be effective in: cutaneous sarcoidosis | Monitoring strategies<br>Baseline renal, liver, and hematological studies<br>Contraindications<br>Pregnancy, lactation, alcohol abuse, liver dysfunction, immunodeficiency syndrome, blood dyscrasias, hypersensitivity to drug<br>Restricted to severe, recalcitrant or disabling psoriasis not adequately responsive to other forms of therapy<br>May be combined with cyclosporine to allow lower doses of both drugs |
| **OCPs** (TriCyclen®, Diane 35®, Alesse®) | 1 pill PO OD | Hormonal acne (chin, jawline)<br>Acne associated with polycystic ovarian syndrome or other endocrine abnormalities | All combined OCPs are helpful in acne but those listed on the left have undergone RCTs<br>Contraindications<br>Smoking, HTN, migraines with aura, pregnancy<br>Routine gynecological health maintenance should be up to date |
| **Spironolactone** | 50-100 mg PO OD alone or with OCPs | Hormonal acne (chin, jawline)<br>Acne with endocrine abnormality | Contraindications<br>Pregnancy<br>Side effects<br>Menstrual irregularities at higher doses if not on OCPs<br>Breast tenderness, mild diuresis common<br>Risk of hyperkalemia – counsel patients to reduce intake of potassium rich foods such as bananas |
| **Terbinafine** (Lamisil®) | 250 mg PO OD x 2 wk<br>Fingernails x 6 wk<br>Toenails x 12 wk<br>Confirm diagnosis prior to treatment | Onychomycosis<br>Tinea corporis, cruris, pedis, capitis | Contraindications<br>Pregnancy, chronic or active liver disease<br>Drug interactions<br>Potent inhibitor of CYP2D6; use with caution when also taking β-blockers, certain anti-arrhythmic agents, MAOI type B, and/or antipsychotics<br>Drug concentrates rapidly in skin, hair, and nails at levels associated with fungicidal activity |
| **Tetracycline** | 250-500 mg PO bid to tid<br>Taken 1 h before or 2 h after a meal | Acne vulgaris<br>Rosacea<br>Bullous pemphigoid | Contraindications<br>Severe renal or hepatic dysfunction |

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# ER Emergency Medicine

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# Acronyms

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| AAA | abdominal aortic aneurysm | DIC | disseminated intravascular coagulation | LPI | umbar puncture | SCI | spinal cord injury |
| ABG | arterial blood gas | DKA | diabetic ketoacidosis | LVH | left ventricular hypertrophy | SJS | Stevens-Johnson syndrome |
| ACS | acute coronary syndrome | DRE | digital rectal exam | MAP | mean arterial pressure | SNS | sympathetic nervous system |
| AED | automatic external defibrillator | DT | delirium tremens | MDI | metred dose inhaler | SOB | shortness of breath |
| AFib | atrial fibrillation | DVT | deep vein thrombosis | MVC | motor vehicle collision | SSSS | staphylococcal scalded skin syndrome |
| AG | anion gap | ED | emergency department | NG | nasogastric | STEMI | ST elevation myocardial infarction |
| ARDS | acute respiratory distress syndrome | EM | erythema multiforme | NS | normal saline | TBI | traumatic brain injury |
| AVN | avascular necrosis | ETT | endotracheal tube | N/V | nausea and vomiting | TCA | tricyclic antidepressant |
| AVPU | alert, voice, pain, unresponsive | FAST | focused abdominal sonogram for trauma | OD | once daily | TEN | toxic epidermal necrolysis |
| AXR | abdominal X-ray | FFP | fresh frozen plasma | PE | pulmonary embolism | TIA | transient ischemic attack |
| Bi-PAP | bilevel positive airway pressure | GERD | gastroesophageal reflux disease | PID | pelvic inflammatory disease | TSS | toxic shock syndrome |
| BSA | body surface area | GCS | glasgow coma scale | PNS | parasympathetic nervous system | U/A | urinalysis |
| CAS | Children's Aid Society | HI | head injury | POG | plasma osmolar gap | U/S | ultrasound |
| CPAP | continuous positive airway pressure | IBD | inflammatory bowel disease | pRBC | packed red blood cells | UTox | urine toxicology screen |
| CPP | cerebral perfusion pressure | IBS | irritable bowel syndrome | RBBB | right bundle branch block | VBG | venous blood gas |
| CSF | cerebrospinal fluid | ICP | intracranial pressure | ROM | range of motion | VFib | ventricular fibrillation |
| CVA | costovertebral angle | ICS | intercostal space | RPS | rapid primary survey | VTach | ventricular tachycardia |
| CXR | chest X-ray | JVP | jugular venous pressure | RSI | rapid sequence induction | VTE | venous thromboembolism |
| D&C | dilatation and curettage | LBBB | left bundle branch block | rt-PA | recombinant tissue plasminogen activator | | |
| DGI | disseminated gonococcal infection | LOC | level of consciousness | SAH | subarachnoid hemorrhage | | |

# Patient Assessment/Management

## 1. Rapid Primary Survey

- **A**irway maintenance with C-spine control
- **B**reathing and ventilation
- **C**irculation (pulses, hemorrhage control)
- **D**isability (neurological status)
- **E**xposure (complete) and **E**nvironment (temperature control)
  - continually reassessed during secondary survey
  - changes in hemodynamic and/or neurological status necessitates a return to the primary survey beginning with airway assessment
- **IMPORTANT**: Always watch for signs of shock while doing primary survey
- addressing the "ABCs" is the hallmark of the emergency department
  - in the setting of cardiac arrest, the approach changes to "the CABs": chest compressions, airway, and breathing
  - CAB can also be applied in massive trauma situations, in the setting of massive blood loss to treat hypovolemic shock

**Approach to the Critically Ill Patient**
1. Rapid Primary Survey (RPS)
2. Resuscitation (often concurrent with RPS)
3. Detailed Secondary Survey
4. Definitive Care

### A. AIRWAY

- first priority is to secure airway
- assume a cervical injury in every trauma patient and immobilize with collar
- assess ability to breathe and speak
- can change rapidly, therefore reassess frequently
- assess for facial fractures/edema/burns (impending airway collapse)

**Signs of Airway Obstruction**
- Agitation, confusion, "universal choking sign"
- Respiratory distress
- Failure to speak, dysphonia, stridor
- Cyanosis

### Airway Management

- anatomic optimization to allow for oxygenation and ventilation

**1. Basic Airway Management**
- protect the C-spine
- head-tilt (if C-spine injury not suspected) or jaw thrust to open the airway
- sweep and suction to clear mouth of foreign material

**2. Temporizing Measures**
- nasopharyngeal airway (if gag reflex present, i.e. conscious)
- oropharyngeal airway (if gag reflex absent, i.e. unconscious)
- "rescue" airway devices (e.g. laryngeal mask airway, Combitube®)
- transtracheal jet ventilation through cricothyroid membrane (last resort)

**3. Definitive Airway Management**
- ETT intubation with in-line stabilization of C-spine
  - orotracheal ± RSI preferred
  - nasotracheal may be better tolerated in conscious patient
- relatively contraindicated with basal skull fracture
  - does not provide 100% protection against aspiration
- surgical airway (if unable to intubate using oral/nasal route and unable to ventilate)
- cricothyroidotomy

**Medications that can be Delivered via ETT**

**NAVEL**
**N**aloxone (Narcan®)
**A**tropine
**V**entolin® (salbutamol)
**E**pinephrine
**L**idocaine

### Contraindications to Intubation

- supraglottic/glottic pathology that would preclude successful intubation

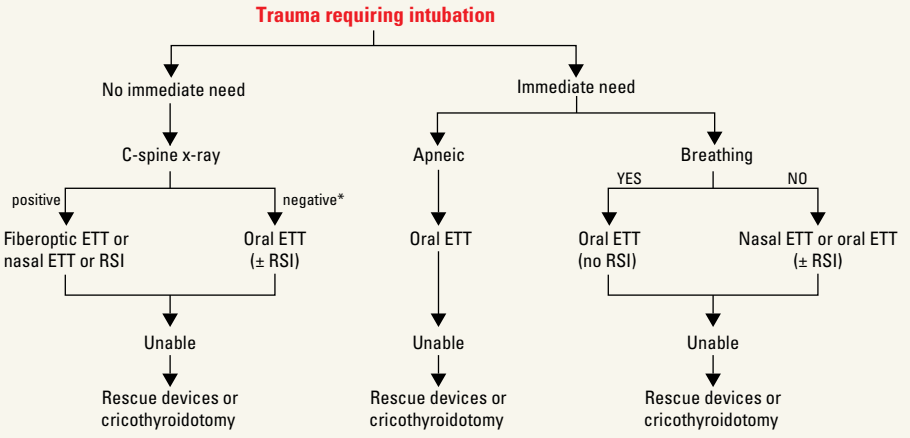



**Figure 1. Approach to endotracheal intubation in an injured patient**

**Indications for Intubation (5 P's)**
- **P**atent airway
- **P**rotects against aspiration
- **P**ositive pressure ventilation
- **P**ulmonary toilet (suction)
- **P**harmacologic administration during hemodynamic instability

**Rescue Techniques in Intubation**
- Bougie (used like a guidewire)
- Glidescope®
- Lighted stylet (uses light through skin to determine if ETT in correct place)
- Fiberoptic intubation – (uses fiberoptic cable for indirect visualization)

## B. BREATHING

- **Look**
  - mental status (anxiety, agitation, decreased LOC), colour, chest movement (bilateral vs. asymmetrical), respiratory rate/effort, nasal flaring
- **Listen**
  - auscultate for signs of obstruction (e.g. stridor), breath sounds, symmetry of air entry, air escaping
- **Feel**
  - tracheal shift, chest wall for crepitus, flail segments, sucking chest wounds, subcutaneous emphysema

Noisy breathing is obstructed breathing until proven otherwise

### Breathing Assessment

- objective measures of respiratory function: rate, oximetry, ABG, A-a gradient

### Management of Breathing

- nasal prongs → simple face mask → non-rebreather mask → CPAP/BiPAP (in order of increasing $FiO_2$)
- Bag-Valve mask and CPAP to supplement inadequate ventilation

**$O_2$ Delivery Methods**

| | $FiO_2$ | Amount Given |
|---|---|---|
| Nasal Prongs | 25-40% | 1-6 L/min |
| Face Mask | 40-60% | 5-10 L/min |
| Non-re-breather | 80-90% | 15 L/min |
| CPAP/ BiPAP | up to 100% | |

## C. CIRCULATION

### Definition of Shock

- inadequate organ and tissue perfusion with oxygenated blood (brain, kidney, extremities)

**Table 1. Major Types of Shock**

| Hypovolemic | Cardiogenic | Distributive (vasodilation) | Obstructive |
|---|---|---|---|
| Hemorrhage (external and internal)<br>Severe burns<br>High output fistulas<br>Dehydration (diarrhea, DKA) | Myocardial ischemia<br>Dysrhythmias<br>CHF<br>Cardiomyopathies<br>Cardiac valve problems | Septic<br>Anaphylactic<br>Neurogenic (spinal cord injury) | Cardiac tamponade<br>Tension pneumothorax<br>PE<br>Aortic stenosis<br>Constrictive pericarditis |

Shock in a trauma patient is hemorrhagic until proven otherwise

### Clinical Evaluation

- early: tachypnea, tachycardia, narrow pulse pressure, reduced capillary refill, cool extremities, and reduced central venous pressure
- late: hypotension and altered mental status, reduced urine output

**Table 2. Estimation of Degree of Hemorrhagic Shock**

| Class | I | II | III | IV |
|---|---|---|---|---|
| **Blood Loss** | <750 cc | 750-1500 cc | 1500-2000 cc | >2000 cc |
| **% of Blood Volume** | <15% | 15-30% | 30-40% | >40% |
| **Pulse** | <100 | >100 | >120 | >140 |
| **Blood Pressure** | Normal | Normal | Decreased | Decreased |
| **Respiratory Rate** | 20 | 30 | 35 | >45 |
| **Capillary Refill** | Normal | Decreased | Decreased | Decreased |
| **Urinary Output** | 30 cc/h | 20 cc/h | 10 cc/h | None |
| **Fluid Replacement** | Crystalloid | Crystalloid | Crystalloid + blood | Crystalloid + blood |

**Causes of Shock**

**SHOCKED**
**S**eptic, spinal/neurogenic
**H**emorrhagic
**O**bstructive (e.g. tension pneumothorax, cardiac tamponade, PE)
**C**ardiogenic (e.g. blunt myocardial injury, dysrhythmia, MI)
anaphylacti**K**
**E**ndocrine (e.g. Addison's, myxedema, coma)
**D**rugs

### Management of Hemorrhagic Shock
- clear airway and assess breathing either first or simultaneously
- apply direct pressure on external wounds while elevating extremities. Do not remove impaled objects in the emergency room setting as they may tamponade bleeds
- start TWO LARGE BORE (14-16G) IVs in the brachial/cephalic vein of each arm
- run 1-2 L bolus of IV Normal Saline/Ringer's Lactate (warmed, if possible)
- if continual bleeding or no response to crystalloids, consider pRBC transfusion, ideally crossmatched. If crossmatched blood is unavailable, consider O- for women of childbearing age and O+ for men. Use FFP, platelets or tranexamic acid in early bleeding
- consider common sites of internal bleeding (abdomen, chest, pelvis, long bones) where surgical intervention may be necessary

**3:1 Rule**
Since only 30% of infused isotonic crystalloids remains in intravascular space, you must give 3x estimated blood loss

### D. DISABILITY
- assess LOC using GCS
- pupils
  - assess equality, size, symmetry, reactivity to light
- unequal or sluggish suggests local eye problem or lateralizing CNS lesion
- relative afferent pupillary defect (swinging light test) – optic nerve damage
  - extraocular movements and nystagmus
  - fundoscopy (papilledema, hemorrhages)
  - reactive pupils + decreased LOC: metabolic or structural cause
  - non-reactive pupils + decreased LOC: structural cause (especially if asymmetric)

**Common Sites of Bleeding**
- External (e.g. scalp)
- Chest
- Abdomen (peritoneum, retroperitoneum)
- Pelvis
- Long bones

### Glasgow Coma Scale
- for use in trauma patients with decreased LOC; good indicator of severity of injury and neurosurgical prognosis
- most useful if repeated; change in GCS with time is more relevant than the absolute number
- less meaningful for metabolic coma
- patient with deteriorating GCS needs immediate attention
- prognosis based on best post-resuscitation GCS
- reported as a 3 part score: Eyes + Verbal + Motor = Total
- if patient intubated, GCS score reported out of 10 + T (T = tubed, i.e. no verbal component)

**Fluid Resuscitation**
- Give bolus until HR decreases, urine output increases, and patient stabilizes
  - Maintenance: 4:2:1 rule
  - 0-10 kg: 4 cc/kg/h
  - 10-20 kg: 2 cc/kg/h
  - Remaining weight: 1 cc/kg/h
  - Replace ongoing losses and deficits (assume 10% of body weight)

**Table 3. Glasgow Coma Scale**

| Eyes Open | | Best Verbal Response | | Best Motor Response | |
|---|---|---|---|---|---|
| Spontaneously | 4 | Answers questions appropriately | 5 | Obeys commands | 6 |
| To voice | 3 | Confused, disoriented | 4 | Localizes to pain | 5 |
| To pain | 2 | Inappropriate words | 3 | Withdraws from pain | 4 |
| No response | 1 | Incomprehensible sounds | 2 | Decorticate (flexion) | 3 |
| | | No verbal response | 1 | Decerebrate (extension) | 2 |
| | | | | No response | 1 |

13-15 = mild injury, 9-12 = moderate injury, ≤8 = severe injury

See Table 36, ER57 for *Modified GCS for infants* and *children*

**Unilateral, Dilated, Non-Reactive Pupil, Think**
- Focal mass lesion
- Epidural hematoma
- Subdural hematoma

### E. EXPOSURE/ENVIRONMENT
- expose patient completely and assess entire body for injury; log roll to examine back
- DRE
- keep patient warm with a blanket ± radiant heaters; avoid hypothermia
- warm IV fluids/blood
- keep providers safe (contamination, combative patient)

## 2. Resuscitation
- done concurrently with primary survey
- attend to ABCs
- manage life-threatening problems as they are identified
- vital signs q5-15 min
- ECG, BP, and $O_2$ monitors
- Foley catheter and NG tube if indicated
- tests and investigations: CBC, electrolytes, BUN, Cr, glucose, amylase, INR/PTT, β-hCG, toxicology screen, cross and type

**Contraindications to Foley Insertion**
- Blood at urethral meatus
- Scrotal hematoma
- High-riding prostate on DRE

**NG Tube Contraindications**
- Significant mid-face trauma
- Basal skull fracture

**Table 4. 2010 AHA CPR Guidelines with 2015 updates**

| Step/Action | Adult: >8 yr | Child: 1-8 yr | Infant: <1 yr |
|---|---|---|---|
| **Airway** | Head tilt-chin lift | | |
| **Breaths** | 2 breaths at 1 s/breath – stop once see chest rise | | |
| **Foreign-Body Airway Obstruction** | Abdominal thrust | | Back slaps and chest thrusts |
| **Compressions** | | | |
| Compression landmarks | In the centre of the chest, between nipples | | Just below nipple line |
| Compression method: push hard and fast, and allow for complete recoil | 2 hands: heel of 1 hand with second hand on top | 2 hands: heel of 1 hand with second on top, or<br>1 hand: heel of 1 hand only | 2 fingers, or thumbs |
| Compression depth | 2-2.4 inches | About 1/3 to 1/2 the depth of the chest | |
| Compression rate | 100-120/min with complete chest wall recoil between compressions | | |
| Compression-ventilation ratio | 30 compressions to 2 ventilations | | |
| Compression-only CPR | Hands-only CPR is preferred if the bystander is not trained or does not feel confident in their ability to provide conventional CPR or if the bystander is trained but chooses to use compressions only | | |
| **Defibrillation** | Immediate defibrillation for all rescuers responding to a sudden witnessed collapse<br>Compressions (5 cycles/2 min) before AED is considered if unwitnessed arrest<br>Manual defibrillators are preferred for children and infants but can use adult dose AED if a manual defibrillator is not available | | |

See Anesthesia and Perioperative Medicine, A32 for *ACLS Guidelines*

# 3. Secondary Survey

- done after primary survey once patient is hemodynamically and neurologically stabilized
- identifies major injuries or areas of concern
- full physical exam and x-rays (C-spine, chest, and pelvis – required in blunt trauma, consider T-spine and L-spine if indicated)

## HISTORY

- "**SAMPLE**": **S**igns and symptoms, **A**llergies, **M**edications, **P**ast medical history, **L**ast meal, **E**vents related to injury

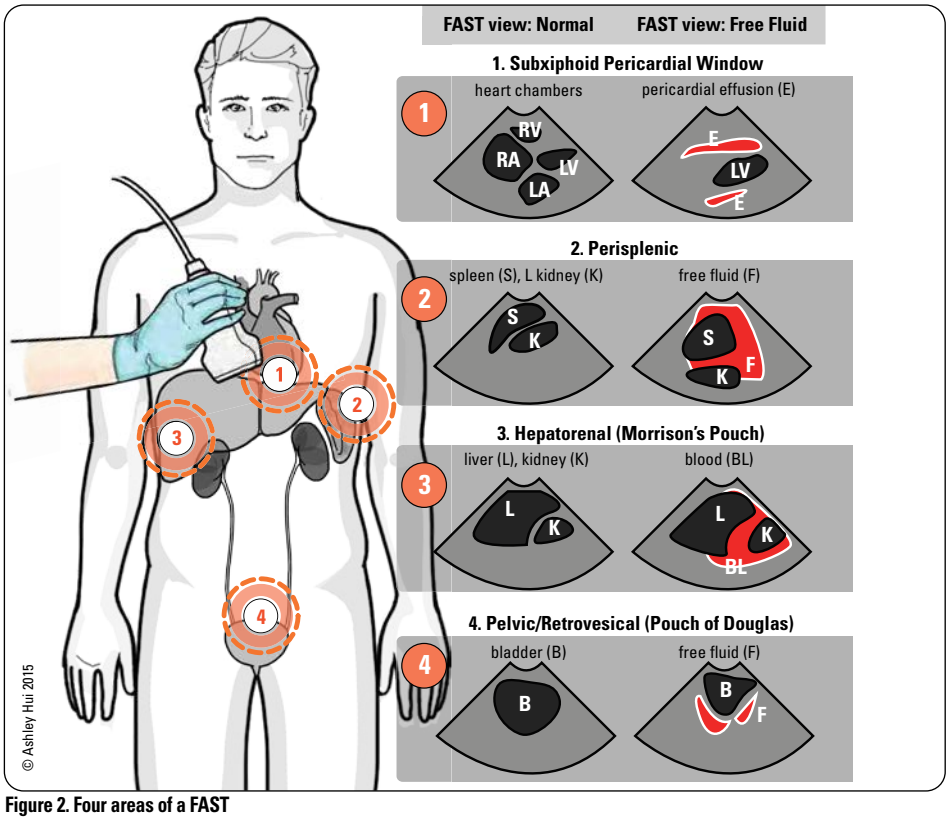



**Figure 2. Four areas of a FAST**

## PHYSICAL EXAM

### Head and Neck
- palpation of facial bones, scalp

### Chest
- inspect for midline trachea and flail segment: ≥2 rib fractures in ≥2 places; if present look for associated hemothorax, pneumothorax, and contusions
- auscultate lung fields
- palpate for subcutaneous emphysema

### Abdomen
- assess for peritonitis, abdominal distention, and evidence of intra-abdominal bleeding
- DRE for GI bleed, high riding prostate, and anal tone

### Musculoskeletal
- examine all extremities for swelling, deformity, contusions, tenderness, ROM
- check for pulses (using Doppler probe) and sensation in all injured limbs
- log roll and palpate thoracic and lumbar spines
- palpate iliac crests and pubic symphysis and assess pelvic stability (lateral, AP, vertical)

### Neurological
- GCS
- full cranial nerve exam
- alterations of rate and rhythm of breathing are signs of structural or metabolic abnormalities with progressive deterioration in breathing indicating a failing CNS
- assess spinal cord integrity
- conscious patient: assess distal sensation and motor function
- unconscious patient: response to painful or noxious stimulus applied to extremities

**Signs of Increased ICP**
- Deteriorating LOC (hallmark)
- Deteriorating respiratory pattern
- Cushing reflex (high BP, low heart rate, irregular respirations)
- Lateralizing CNS signs (e.g. cranial nerve palsies, hemiparesis)
- Seizures
- Papilledema (occurs late)
- N/V and headache

## INITIAL IMAGING
- non-contrast CT head/face/C-spine (rule out fractures and bleeds)
- chest x-ray
- FAST (see Figure 2) or CT abdomen/pelvis (if stable)
- pelvis x-ray

Non-contrast head CT is the best imaging modality for intracranial injury

# Ethical Considerations

### Consent to Treatment: Adults
- see Ethical, Legal, and Organizational Medicine, ELOM7
- Emergency Rule: consent is not needed when a patient is at imminent risk from a serious injury AND obtaining consent is either: a) not possible, OR b) would increase risk to the patient
  - assumes that most people would want to be saved in an emergency
- any capable and informed patient can refuse treatment or part of treatment, even if it is life-saving
- exceptions to the Emergency Rule – treatment cannot be initiated if:
  - a competent patient has previously refused the same or similar treatment and there is no evidence to suggest the patient's wishes have changed
  - an advanced directive is available (e.g. do not resuscitate order)
  - NOTE: refusal of help in a suicide situation is NOT an exception; care must be given
- if in doubt, initiate treatment
- care can be withdrawn if necessary at a later time or if wishes are clarified by family

### Consent to Treatment: Children
- treat immediately if patient is at imminent risk
- parents/guardians have the right to make treatment decisions
- if parents refuse treatment that is life-saving or will potentially alter the child's quality of life, CAS must be contacted – consent of CAS is needed to treat

### Other Issues of Consent
- need consent for HIV testing, as well as for administration of blood products
- however, if delay in substitute consent for blood transfusions puts patient at risk, transfusions can be given

### Duty to Report
- law may vary depending on province and/or state
- examples: gunshot wounds, suspected child abuse, various communicable diseases, medical unsuitability to drive, risk of substantial harm to others

**Jehovah's Witnesses**
- Capable adults have the right to refuse medical treatment
- May refuse whole blood, pRBCs, platelets, and plasma even if life-saving
- Should be questioned directly about the use of albumin, immunoglobulins, hemophilic preparations
- Do not allow autologous transfusion unless there is uninterrupted extra corporeal circulation
- Usually ask for the highest possible quality of care without the use of the above interventions (e.g. crystalloids for volume expansion, attempts at bloodless surgery)
- Patient will generally sign hospital forms releasing medical staff from liability
- Most legal cases involve children of Jehovah's Witnesses; if life-saving treatment is refused, contact CAS

# Traumatology

- epidemiology
  - leading cause of death in patients <45 yr
  - 4th highest cause of death in North America
  - causes more deaths in children/adolescents than all diseases combined
- trimodal distribution of death
  - minutes: death usually at the scene from lethal injuries
  - early: death within 4-6 h – "golden hour" (decreased mortality with trauma care)
  - days-weeks: death from multiple organ dysfunction, sepsis, VTE, etc.
- injuries fall into two categories
  - blunt (most common): MVC, pedestrian-automobile impact, motorcycle collision, fall, assault, sports
  - penetrating (increasing in incidence): gunshot wound, stabbing, impalement



Always completely expose and count the number of wounds

## Considerations for Traumatic Injury

- important to know the mechanism of injury to anticipate traumatic injuries
- always look for an underlying cause (alcohol, medications, illicit substances, seizure, suicide attempt, medical problem)
- always inquire about HI, loss of consciousness, amnesia, vomiting, headache, and seizure activity



**Cardiac Box:** sternal notch, nipples, and xiphoid process; injuries inside this area should increase suspicion of cardiac injury

**Table 5. Mechanisms and Considerations of Traumatic Injuries**

| Mechanism of Injury | Special Considerations | Associated Injuries |
|---|---|---|
| **MVC** | Vehicle(s) involved: weight, size, speed, damage<br>Location of patient in vehicle<br>Use and type of seatbelt<br>Ejection of patient from vehicle<br>Entrapment of patient under vehicle<br>Airbag deployment<br>Helmet use in motorcycle collision | Head-on collision: head/facial, thoracic (aortic), lower extremity<br>Lateral/T-bone collision: head, C-spine, thoracic, abdominal, pelvic, and lower extremity<br>Rear-end collision: hyper-extension of C-spine (whiplash injury)<br>Rollover |
| **Pedestrian-Automobile Impact** | High morbidity and mortality<br>Vehicle speed is an important factor<br>Site of impact on car | Children at increased risk of being run over (multisystem injuries)<br>Adults tend to be struck in lower legs (lower extremity injuries), impacted against car (truncal injuries), and thrown to ground (HI) |
| **Falls** | 1 storey = 12 ft = 3.6 m<br>Distance of fall: 50% mortality at 4 storeys and 95% mortality at 7 storeys<br>Landing position (vertical vs. horizontal) | Vertical: lower extremity, pelvic, and spine fractures; HI<br>Horizontal: facial, upper extremity, and rib fractures; abdominal, thoracic, and HI |



**High Risk Injuries**
- MVC at high speed, resulting in ejection from vehicle
- Motorcycle collisions
- Vehicle vs. pedestrian crashes
- Fall from height >12 ft (3.6 m)



**Vehicle vs. Pedestrian Crash**
In adults look for triad of injuries (Waddle's triad)
- Tibia-fibula or femur fracture
- Truncal injury
- Craniofacial injury

## Head Trauma



- see Neurosurgery, NS30
- 60% of MVC-related deaths are due to HI

### Specific Injuries

- **fractures**
  - Dx: non-contrast head CT and physical exam

A. skull fractures
- vault fractures
  - linear, non-depressed
    - most common
    - typically occur over temporal bone, in area of middle meningeal artery (commonest cause of epidural hematoma)
  - depressed
    - open (associated overlying scalp laceration and torn dura, skull fracture disrupting paranasal sinuses or middle ear) vs. closed
- basal skull fractures
  - typically occur through floor of anterior cranial fossa (longitudinal more common than transverse)
  - generally a clinical diagnosis (poorly visualized on CT)
  - associated with battle signs or racoon eyes

B. facial fractures (see Plastic Surgery, PL31)
- neuronal injury
- beware of open fracture or sinus fractures (risk of infection)
- severe facial fractures may pose risk to airway from profuse bleeding



**Signs of Basal Skull Fracture**
- Battle's sign (bruised mastoid process)
- Hemotympanum
- Raccoon eyes (periorbital bruising)
- CSF rhinorrhea/otorrhea

- **scalp laceration**
  - can be a source of significant bleeding
  - achieve hemostasis, inspect and palpate for skull bone defects ± CT head (rule-out skull fracture)
- **neuronal injury**

A. diffuse
- mild TBI = concussion
  - transient alteration in mental status that may involve loss of consciousness
  - hallmarks of concussion: confusion and amnesia, which may occur immediately after the trauma or minutes later
  - loss of consciousness (if present) must be less than 30 min, initial GCS must be between 13-15, and post-traumatic amnesia must be less than 24 h
- diffuse axonal injury
  - mild: coma 6-24 h, possibly lasting deficit
  - moderate: coma >24 h, little or no signs of brainstem dysfunction
  - severe: coma >24 h, frequent signs of brainstem dysfunction

B. focal injuries
- contusions
- intracranial hemorrhage (epidural, subdural, intracerebral)

## ASSESSMENT OF BRAIN INJURY

### History
- pre-hospital status
- mechanism of injury

### Physical Exam
- assume C-spine injury until ruled out
- vital signs
  - shock (not likely due to isolated brain injury, except in infants)
  - Cushing's response to increasing ICP (bradycardia, HTN, irregular respirations)
- severity of injury determined by

1. LOC
   - GCS ≤8 intubate, any change in score of 3 or more = serious injury
   - mild TBI = 13-15, moderate = 9-12, severe = 3-8
2. pupils: size, anisocoria >1 mm (in patient with altered LOC), response to light
3. lateralizing signs (motor/sensory)
   - may become subtler with increasing severity of injury
   - reassess frequently

**Warning Signs of Severe Head Injury**
- GCS <8
- Deteriorating GCS
- Unequal pupils
- Lateralizing signs

**N.B.** Altered LOC is a hallmark of brain injury

### Investigations
- labs: CBC, electrolytes, INR/PTT, glucose, toxicology screen
- CT scan head and neck (non-contrast) to exclude intracranial hemorrhage/hematoma
- C-spine imaging

**Canadian CT Head Rule**
Lancet 2001;357:1391-96

**CT Head is only required for patients with minor HI with any one of the following**

**High Risk** (for neurological intervention)
- GCS score <15 at 2 h after injury
- Suspected open or depressed skull fracture
- Any sign of basal skull fracture (hemotympanum, "raccoon" eyes, CSF otorrhea/rhinorrhea, Battle's sign)
- Vomiting ≥2 episodes
- Age ≥65 yr

**Medium Risk** (for brain injury on CT)
- Amnesia before impact >30 min (i.e. cannot recall events just before impact)
- Dangerous mechanism (pedestrian struck by MVC, occupant ejected from motor vehicle, fall from height >3 ft or five stairs)

**Minor HI** is defined as witnessed loss of consciousness, definite amnesia, or witnessed disorientation in a patient with a GCS score of 13-15.

**NB:** Canadian CT Head Rule does not apply for non-trauma cases, for GCS<13, age <16, for patients on Coumadin® and/or having a bleeding disorder, or having an obvious open skull fracture.

### Management
- goal in ED: reduce secondary injury by avoiding hypoxia, ischemia, decreased CPP, seizure
- general
  - ABCs
  - ensure oxygen delivery to brain through intubation and prevent hypercarbia
  - maintain BP (sBP >90)
  - treat other injuries
- early neurosurgical consultation for acute and subsequent patient management
- seizure treatment/prophylaxis
  - benzodiazepines, phenytoin, phenobarbital
  - steroids are of no proven value
- treat suspected raised ICP, consider if HI with signs of increased ICP:
  - intubate
  - calm (sedate) if risk for high airway pressures or agitation
  - paralyze if agitated
  - hyperventilate (100% $O_2$) to a $pCO_2$ of 30-35 mmHg
  - elevate head of bed to 20°
  - adequate BP to ensure good cerebral perfusion
  - diurese with mannitol 1g/kg infused rapidly (contraindicated in shock/renal failure)

### Disposition
- neurosurgical ICU admission for severe HI
- in hemodynamically unstable patient with other injuries, prioritize most life-threatening injuries and maintain cerebral perfusion
- for minor HI not requiring admission, provide 24 h HI protocol to competent caregiver, follow-up with neurology as even seemingly minor HI may cause lasting deficits

# Mild Traumatic Brain Injury

### Epidemiology
- TBI results in 1.7 million deaths, hospitalizations, and ED visits each year (US)
- 75% are estimated to be mild TBI; remainder are moderate or severe (see Neurosurgery, NS31)
- highest rates in children 0-4 yr, adolescents 15-19 yr, and elderly >65 yr

### Clinical Features
- somatic: headache, sleep disturbance, N/V, blurred vision
- cognitive dysfunction: attentional impairment, reduced processing speed, drowsiness, amnesia
- emotion and behaviour: impulsivity, irritability, depression
- severe concussion: may precipitate seizure, bradycardia, hypotension, sluggish pupils

Extent of retrograde amnesia correlates with severity of injury

### Etiology
- falls, MVC, struck by an object, assault, sports

### Investigations
- neurological exam
- concussion recognition tool (see thinkfirst.ca)
- imaging – CT as per Canadian CT Head Rules, or MRI if worsening symptoms despite normal CT

**Every Patient with One or More of the Following Signs or Symptoms should be Placed in a C-Spine Collar**
- Midline tenderness
- Neurological symptoms or signs
- Significant distracting injuries
- HI
- Intoxication
- Dangerous mechanism
- History of altered LOC

### Treatment
- close observation and follow-up; for patients at risk of intracranial complications, give appropriate discharge instructions to patient and family; watch for changes to clinical features above, and if change, return to ED
- hospitalization with normal CT (GCS <15, seizures, bleeding diathesis), or with abnormal CT
- pharmacological management of pain, depression, headache
- follow Return to Play guidelines

### Prognosis
- most recover with minimal treatment
  - athletes with previous concussion are at increased risk of cumulative brain injury
- repeat TBI can lead to life-threatening cerebral edema or permanent impairment

# Spine and Spinal Cord Trauma

- assume cord injury with significant falls (>12 ft), deceleration injuries, blunt trauma to head, neck, or back
- spinal immobilization (cervical collar, spine board during patient transport only) must be maintained until spinal injury has been ruled out (see Figure 3)
- vertebral injuries may be present without spinal cord injury; normal neurologic exam does not exclude spinal injury
- cord may be injured despite normal C-spine x-ray (spinal cord injury without radiologic abnormality)
- injuries can include: complete/incomplete transection, cord edema, spinal shock

Of the investigations, the lateral C-spine x-ray is the single most important film; 95% of radiologically visible abnormalities are found on this film

### History
- mechanism of injury, previous deficits, SAMPLE
- neck pain, paralysis/weakness, paresthesia

Cauda Equina Syndrome can occur with any spinal cord injury below T10 vertebrae. Look for incontinence, anterior thigh pain, quadriceps weakness, abnormal sacral sensation, decreased rectal tone, and variable reflexes

### Physical Exam
- ABCs
- abdominal: ecchymosis, tenderness
- neurological: complete exam, including mental status
- spine: maintain neutral position, palpate C-spine; log roll, then palpate T-spine and L-spine, assess rectal tone
  - when palpating, assess for tenderness, muscle spasm, bony deformities, step-off, and spinous process malalignment
- extremities: check capillary refill, suspect thoracolumbar injury with calcaneal fractures

### Investigations
- bloodwork: CBC, electrolytes, Cr, glucose, coagulation profile, cross and type, toxicology screen
- imaging
  - full C-spine x-ray series for trauma (AP, lateral, odontoid)
- thoracolumbar x-rays
  - AP and lateral views

**The Canadian C-Spine Rule vs. the NEXUS Low-Risk Criteria in Patients with Trauma**
NEJM 2003;349:2510-18
**Purpose:** To compare the clinical performance of the Canadian C-Spine Rule (CCR) and the National Emergency X-Radiography Utilization Study (NEXUS) Low-Risk Criteria (NLC).

**Study:** Trauma patients (n=8283) in stable condition were prospectively evaluated by both the CCR and NLC by 394 physicians before radiography. 2% of these patients had a C-spine injury.
**Results:** Compared to the NLC, the CCR was more sensitive (99.4 vs. 90.7%) and more specific (45.1 vs. 36.8%) after exclusion of indeterminate cases. The number of missed patients would be 1 for the CCR and 16 for the NLC. The ROM was not evaluated in some CCR cases likely because physicians were not comfortable with the procedure and this may slightly lower the sensitivity or specificity of the CCR in practice.
**Summary:** The CCR is superior to the NLC in alert and stable patients with trauma. The use of the CCR can result in lower radiography rates.

- indications
  - C-spine injury
  - unconscious patients (with appropriate mechanism of injury)
  - neurological symptoms or findings
  - deformities that are palpable when patient is log rolled
  - back pain
  - bilateral calcaneal fractures (due to fall from height)
    - concurrent burst fractures of the lumbar or thoracic spine in 10% (T11-L2)
  - consider CT (for subtle bony injuries), MRI (for soft tissue injuries) if appropriate

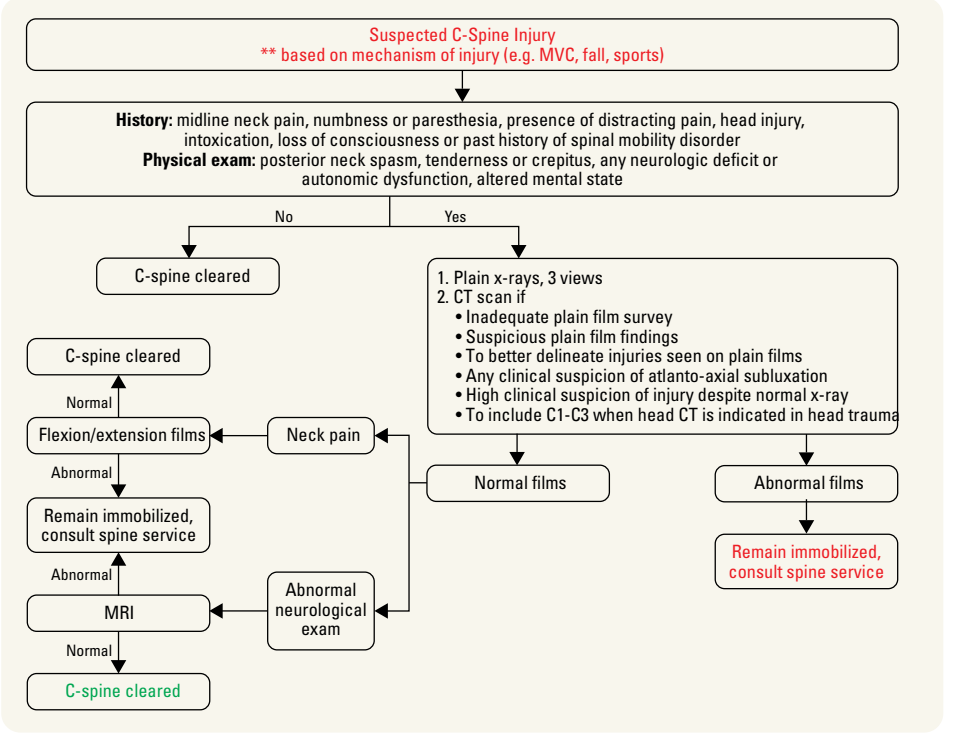
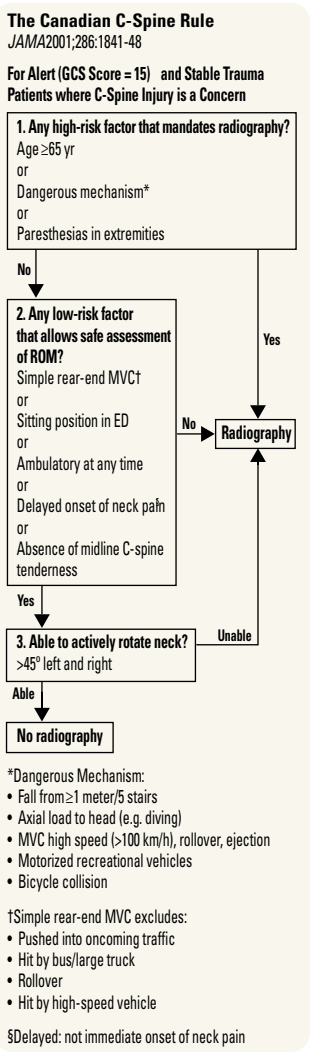



**Figure 3. Approach to clearing the C-spine**




## Can Clear C-Spine if:

- oriented to person, place, time, and event
- no evidence of intoxication
- no posterior midline cervical tenderness
- no focal neurological deficits
- no painful distracting injuries (e.g. long bone fracture)

## Management of Cord Injury

- immobilize
- evaluate ABCs
- treat neurogenic shock (maintain sBP >100 mmHg)
- insert NG and Foley catheter
- complete imaging of spine and consult spine service if available
- continually reassess high cord injuries as edema can travel up cord
- if cervical cord lesion, watch for respiratory insufficiency
  - low cervical transection (C5-T1) produces abdominal breathing (phrenic innervation of diaphragm still intact but loss of innervation of intercostals and other accessory muscles of breathing)
  - high cervical cord injury (above C4) may require intubation and ventilation
- treatment: warm blanket, Trendelenburg position (occasionally), volume infusion, consider vasopressors

## Approach to C-Spine X-Rays

- 3-view C-spine series is the screening modality of choice
  1. lateral C1-T1 ± swimmer's view
     - lateral view is best, identifies 90-95% of injuries
  2. odontoid view (open mouth or oblique submental view)
     - examine the dens for fractures
       - if unable to rule out fracture, repeat view or consider CT or plain film tomography
     - examine lateral aspects of C1 and spacing relative to C2

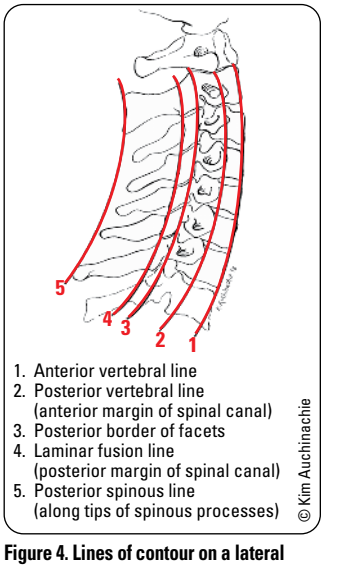


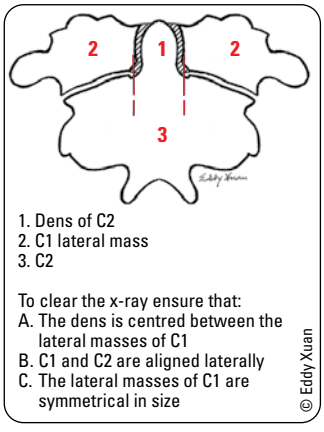

**Figure 4. Lines of contour on a lateral C-spine x-ray**

Prevertebral soft tissue swelling is only 49% sensitive for injury

3. AP view
   - alignment of spinous processes in the midline
   - spacing of spinous processes should be equal
   - check vertebral bodies and facet dislocations

**Table 6. Interpretation of Lateral View: The ABCS**

| | |
|---|---|
| **A** | **Adequacy and Alignment**<br>Must see C1 to C7-T1 junction; if not, downward traction of shoulders, swimmer's view, bilateral supine obliques, or CT scan needed<br>Lines of contour in children <8 yr of age, can see physiologic subluxation of C2 on C3, and C3 on C4, but the spino-laminal line is maintained<br>Fanning of spinous processes suggests posterior ligamentous disruption<br>Widening of facet joints<br>Check atlanto-occipital joint<br>Line extending inferiorly from clivus should transect odontoid<br>Atlanto-axial articulation, widening of predental space (normal: <3 mm in adults, <5 mm in children) indicates injury of C1 or C2 |
| **B** | **Bones**<br>Height, width, and shape of each vertebral body<br>Pedicles, facets, and laminae should appear as one – doubling suggests rotation |
| **C** | **Cartilage**<br>Intervertebral disc spaces – wedging anteriorly or posteriorly suggests vertebral compression |
| **S** | **Soft Tissues**<br>Widening of retropharyngeal (normal: <7 mm at C1-4, may be wide in children <2 yr on expiration) or retrotracheal spaces (normal: <22 mm at C6-T1, <14 mm in children <5 yr) |




1. Dens of C2
2. C1 lateral mass
3. C2

To clear the x-ray ensure that:
A. The dens is centred between the lateral masses of C1
B. C1 and C2 are aligned laterally
C. The lateral masses of C1 are symmetrical in size

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**Figure 5. C-spine x-ray; odontoid view**

## Sequelae of C-Spine Fractures

- see Neurosurgery, NS34
- acute phase of SCI
  - spinal shock: absence of all voluntary and reflex activity below level of injury
    - decreased reflexes, no sensation, flaccid paralysis below level of injury, lasting days to months
  - neurogenic shock: loss of vasomotor tone, SNS tone
    - watch for: hypotension (lacking SNS), bradycardia (unopposed PNS), poikilothermia (lacking SNS so no shunting of blood from extremities to core)
    - occurs within 30 min of SCI at level T6 or above, lasting up to 6 wk
    - provide airway support, fluids, atropine (for bradycardia), vasopressors for BP support
- chronic phase of SCI
  - autonomic dysreflexia: in patients with an SCI at level T6 or above
    - signs and symptoms: pounding headache, nasal congestion, feeling of apprehension or anxiety, visual changes, dangerously increased sBP and dBP
    - common triggers
      - GU causes: bladder distention, urinary tract infection, and kidney stones
      - GI causes: fecal impaction or bowel distension
    - treatment: monitoring and controlling BP, prior to addressing causative issue

**Supine Oblique Views**
- Rarely used
- Better visualization of posterior element fractures (lamina, pedicle, facet joint)
- Good to assess patency of neural foramina
- Can be used to visualize the C7-T1 junction

20% of C-spine fractures are accompanied by other spinal fractures, so ensure thoracic and lumbar spine x-rays are normal before proceeding to OR

# Chest Trauma

- two types: those found and managed in 1° survey and those found and managed in 2° survey

**Table 7. Life-Threatening Chest Injuries Found in 1° Survey**

| | Physical Exam | Investigations | Management |
|---|---|---|---|
| **Airway Obstruction** | Anxiety, stridor, hoarseness, altered mental status<br>Apnea, cyanosis | Do not wait for ABG to intubate | Definitive airway management<br>Intubate early<br>Remove foreign body if visible with laryngoscope prior to intubation |
| **Tension Pneumothorax**<br>Clinical diagnosis<br>One-way valve causing accumulation of air in pleural space | Respiratory distress, tachycardia, distended neck veins, cyanosis, asymmetry of chest wall motion<br>Tracheal deviation away from pneumothorax<br>Percussion hyperresonance<br>Unilateral absence of breath sounds | Non-radiographic diagnosis | Needle thoracostomy – large bore needle, 2nd ICS mid clavicular line, followed by chest tube in 5th ICS, anterior axillary line |

Trauma to the chest accounts for 50% of trauma deaths

80% of all chest injuries can be managed non-surgically with simple measures such as intubation, chest tubes, and pain control

**Table 7. Life-Threatening Chest Injuries Found in 1º Survey** (continued)

| | Physical Exam | Investigations | Management |
|---|---|---|---|
| **Open Pneumothorax**<br>Air entering chest from wound rather than trachea | Gunshot or other wound (hole >2/3 tracheal diameter) ± exit wound<br>Unequal breath sounds | ABG: decreased $pO_2$ | Air-tight dressing sealed on 3 sides<br>Chest tube<br>Surgery |
| **Massive Hemothorax**<br>>1500 cc blood loss in chest cavity | Pallor, flat neck veins, shock<br>Unilateral dullness<br>Absent breath sounds<br>Hypotension | Usually only able to do supine CXR – entire lung appears radioopaque as blood spreads out over posterior thoracic cavity | Restore blood volume<br>Chest tube<br>Thoracotomy if:<br>>1500 cc total blood loss<br>≥200 cc/h continued drainage |
| **Flail Chest**<br>Free-floating segment of chest wall due to >2 rib fractures, each at 2 sites<br>Underlying lung contusion (cause of morbidity and mortality) | Paradoxical movement of flail segment<br>Palpable crepitus of ribs<br>Decreased air entry on affected side | ABG: decreased $pO_2$, increased $pCO_2$<br>CXR: rib fractures, lung contusion | $O_2$ + fluid therapy + pain control<br>Judicious fluid therapy in absence of systemic hypotension<br>Positive pressure ventilation ± intubation and ventilation |
| **Cardiac Tamponade**<br>Clinical diagnosis<br>Pericardial fluid accumulation impairing ventricular function | Penetrating wound (usually)<br>Beck's triad: hypotension, distended neck veins, muffled heart sounds<br>Tachycardia, tachypnea<br>Pulsus paradoxus<br>Kussmaul's sign (increased JVP with inspiration) | Echocardiogram<br>FAST | IV fluids<br>Pericardiocentesis<br>Open thoracotomy |

**3-way Seal for Open Pneumothorax (i.e. sucking chest wound)**
Allows air to escape during the expiratory phase (so that you do not get a tension pneumothorax) but seals itself to allow adequate breaths during the inspiratory phase

**Pulsus Paradoxus:** a drop in BP of >10 mmHg with inspiration. Recall that BP normally drops with inspiration, but what's "paradoxical" about this is that it drops more than it should

**Table 8. Potentially Life-Threatening Chest Injuries Found in 2º Survey**

| | Physical Exam | Investigations | Management |
|---|---|---|---|
| **Pulmonary Contusion** | Blunt trauma to chest<br>Interstitial edema impairs compliance and gas exchange | CXR: areas of opacification of lung within 6 h of trauma | Maintain adequate ventilation<br>Monitor with ABG, pulse oximeter, and ECG<br>Chest physiotherapy<br>Positive pressure ventilation if severe |
| **Ruptured Diaphragm** | Blunt trauma to chest or abdomen (e.g. high lap belt in MVC) | CXR: abnormality of diaphragm/lower lung fields/NG tube placement<br>CT scan and endoscopy: sometimes helpful for diagnosis | Laparotomy for diaphragm repair and associated intra-abdominal injuries |
| **Esophageal Injury** | Usually penetrating trauma (pain out of proportion to degree of injury) | CXR: mediastinal air (not always)<br>Esophagram (Gastrografin®)<br>Flexible esophagoscopy | Early repair (within 24 h) improves outcome but all require repair |
| **Aortic Tear**<br>90% tear at subclavian (near ligamentum arteriosum), most die at scene<br>Salvageable if diagnosis made rapidly | Sudden high speed deceleration (e.g. MVC, fall, airplane crash), complaints of chest pain, dyspnea, hoarseness (frequently absent)<br>Decreased femoral pulses, differential arm BP (arch tear) | CXR, CT scan, transesophageal echo, aortography (gold standard) | Thoracotomy (may treat other severe injuries first) |
| **Blunt Myocardial Injury (rare)** | Blunt trauma to chest (usually in setting of multi-system trauma and therefore difficult to diagnose)<br>Physical exam: overlying injury e.g. fractures, chest wall contusion | ECG: dysrhythmias, ST changes<br>Patients with a normal ECG and normal hemodynamics never get dysrhythmias | $O_2$<br>Antidysrhythmic agents<br>Analgesia |

Ruptured diaphragm is more often diagnosed on the left side, as liver conceals right side defect

**Aortic Tear**

**ABC WHITE**
X-ray features of **A**ortic tear
Depressed left mainstem **B**ronchus
pleural **C**ap
**W**ide mediastinum (most consistent)
**H**emothorax
**I**ndistinct aortic knuckle
**T**racheal deviation to right side
**E**sophagus (NG tube) deviated to right
(Note: present in 85% of cases, but cannot rule out)

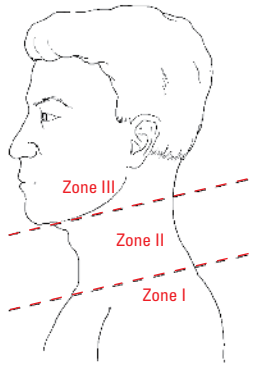
**If Penetrating Neck Trauma Present, DON'T:**
- Clamp structures (can damage nerves)
- Probe
- Insert NG tube (leads to bleeding)
- Remove weapon/impaled object

## Other Potentially Life-Threatening Injuries Related to the Chest

### Penetrating Neck Trauma

- includes all penetrating trauma to the three zones of the neck
- management: injuries deep to platysma require further evaluation by angiography, contrast CT, or surgery
- do not explore penetrating neck wounds except in the OR

### Airway Injuries
- always maintain a high index of suspicion
- larynx
  - history: strangulation, direct blow, blunt trauma, any penetrating injury involving platysma
  - triad: hoarseness, subcutaneous emphysema, palpable fracture
  - other symptoms: hemoptysis, dyspnea, dysphonia
  - investigations: CXR, CT scan, arteriography (if penetrating)
  - management
    - airway: manage early because of edema
    - C-spine may also be injured, consider mechanism of injury
    - surgical: tracheotomy vs. repair
- trachea/bronchus
  - frequently missed
  - history: deceleration, penetration, increased intra-thoracic pressure, complaints of dyspnea, hemoptysis
  - examination: subcutaneous air, Hamman's sign (crunching sound synchronous with heart beat)
  - CXR: mediastinal air, persistent pneumothorax or persistent air leak after chest tube inserted for pneumothorax
  - management
    - surgical repair if >1/3 circumference




**Zone III:** Superior aspect of neck
**Zone II:** Midportion of neck (cricoid to the angle of mandible)
**Zone I:** Base of neck (thoracic inlet to cricoid cartilage)

**Figure 6. Zones of the neck in trauma**

## Abdominal Trauma

- two mechanisms
  - blunt: usually causes solid organ injury (spleen = most common, liver = 2nd)
  - penetrating: usually causes hollow organ injury or liver injury (most common)

### BLUNT TRAUMA
- results in two types of hemorrhage: intra-abdominal and retroperitoneal
- adopt high clinical suspicion of bleeding in multi-system trauma

### History
- mechanism of injury, SAMPLE history

### Physical Exam
- often unreliable in multi-system trauma, wide spectrum of presentations
  - slow blood loss not immediately apparent
  - tachycardia, tachypnea, oliguria, febrile, hypotension
  - other injuries may mask symptoms
  - serial examinations are required
- abdomen
  - inspect: contusions, abrasions, seat-belt sign, distention
  - auscultate: bruits, bowel sounds
  - palpate: tenderness, rebound tenderness, rigidity, guarding
  - DRE: rectal tone, blood, bone fragments, prostate location
  - placement of NG, Foley catheter should be considered part of the abdominal exam
- other systems to assess: cardiovascular, respiratory (possibility of diaphragm rupture), genitourinary, pelvis, back/neurological

### Investigations
- labs: CBC, electrolytes, coagulation, cross and type, glucose, Cr, CK, lipase, amylase, liver enzymes, ABG, blood EtOH, β-hCG, U/A, toxicology screen

**Table 9. Imaging in Abdominal Trauma**

| Imaging | Strengths | Limitations |
|---|---|---|
| **X-Ray** | Chest (looking for free air under diaphragm, diaphragmatic hernia, air-fluid levels), pelvis, cervical, thoracic, lumbar spines | Soft tissue not well visualized |
| **CT Scan** | Most specific test | Radiation exposure 20x more than x-ray<br>Cannot use if hemodynamic instability |
| **Diagnostic Peritoneal Lavage (rarely used)** | Most sensitive test<br>Tests for intra-peritoneal bleed | Cannot test for retroperitoneal bleed or diaphragmatic rupture<br>Cannot distinguish lethal from trivial bleed<br>Results can take up to 1 h |
| **Ultrasound: FAST** | Identifies presence/absence of free fluid in peritoneal cavity<br>RAPID exam: less than 5 min<br>Can also examine pericardium and pleural cavities | NOT used to identify specific organ injuries<br>If patient has ascites, FAST will be falsely positive |

**Seatbelt Injuries May Cause**
- Retroperitoneal duodenal trauma
- Intraperitoneal bowel transection
- Mesenteric injury
- L-spine injury

**Indications for Foley and NG Tube in Abdominal Trauma**

**Foley catheter:** unconscious or patient with multiple injuries who cannot void spontaneously or is unconscious
**NG tube:** used to decompress the stomach and proximal small bowel. Contraindicated if suspected facial or basal skull fractures

**Criteria for Positive Lavage**
- >10 cc gross blood
- Bile, bacteria, foreign material
- RBC count >100,000 x $10^6$/L
- WBC >500 x $10^6$/L,
- Amylase >175 IU

**Point-of-care ultrasonography for diagnosing thoracoabdominal injuries in patients with blunt trauma**
Cochrane DB Syst Rev 2018:CD012669
**Objectives**: Determine the diagnostic accuracy of POCUS for detecting and excluding free fluid, organ injuries, vascular lesions, and other injuries compared to diagnostic reference standard in patients with blunt trauma.
**Methods**: Systematic review of prospective or retrospective diagnostic cohort studies of patients with any type of blunt trauma.
**Results**: 34 studies, 8635 participants. For abdominal trauma, POCUS had a sensitivity of 0.68 (95% CI 0.59-0.75) and a specificity of 0.95 (95% CI 0.92-0.97). In children, pooled sensitivity of POCUS was 0.63 (95% CI 0.46-0.77), as compared to 0.78 (95% CI 0.69-0.84) in an adult/mixed population. For chest injuries, POCUS had a sensitivity of 0.96 (95% CI 0.88-0.99) and a specificity of 0.95 (95% CI 0.97-1.00).
**Conclusions**: In patients with blunt thoracoabdominal trauma, positive POCUS findings are helpful for guiding treatment decisions. However, with regard to abdominal trauma, a negative POCUS does not rule out injuries and must be verified. This is of particular importance in paediatric trauma, where the sensitivity of POCUS is poor. Based on a small number of studies in a mixed population, POCUS may have a higher sensitivity in chest injuries.

- imaging must be done if:
  - equivocal abdominal examination, altered sensorium, or distracting injuries (e.g. head trauma, spinal cord injury resulting in abdominal anesthesia)
  - unexplained shock/hypotension
  - patients have multiple traumas and must undergo general anesthesia for orthopedic, neurosurgical, or other injuries
  - fractures of lower ribs, pelvis, spine
  - positive FAST

### Management
- general: ABCs, fluid resuscitation, and stabilization
- surgical: watchful waiting vs. laparotomy
- solid organ injuries: decision based on hemodynamic stability, not the specific injuries
- hemodynamically unstable or persistently high transfusion requirements: laparotomy
- hollow organ injuries: laparotomy
- even if low suspicion of injury: admit and observe for 24 h

**Laparotomy is Mandatory if Penetrating Trauma and:**
- Shock
- Peritonitis
- Evisceration
- Free air in abdomen
- Blood in NG tube, Foley catheter, or on DRE

### PENETRATING TRAUMA
- high risk of gastrointestinal perforation and sepsis
- history: size of blade, calibre/distance from gun, route of entry
- local wound exploration under direct vision may determine lack of peritoneal penetration (not reliable in inexperienced hands) with the following exceptions:
  - thoracoabdominal region (may cause pneumothorax)
  - back or flanks (muscles too thick)

**"Rule of Thirds" for Stab Wounds**
- 1/3 do not penetrate peritoneal cavity
- 1/3 penetrate but are harmless
- 1/3 cause injury requiring surgery

### Management
- general: ABCs, fluid resuscitation, and stabilization
- gunshot wounds always require laparotomy

## Genitourinary Tract Injuries

- see Urology, U34

### Etiology
- blunt trauma: often associated with pelvic fractures
  - upper tract
    - renal
      - contusions (minor injury – parenchymal ecchymoses with intact renal capsule)
      - parenchymal tears/laceration: non-communicating (hematoma) vs. communicating (urine extravasation, hematuria)
    - ureter: rare, at uretero-pelvic junction
  - lower tract
    - bladder
      - extraperitoneal rupture of bladder from pelvic fracture fragments
      - intraperitoneal rupture of bladder from trauma and full bladder
    - urethra
      - posterior urethral injuries: MVCs, falls, pelvic fractures
      - anterior urethral injuries: blunt trauma to perineum, straddle injuries/direct strikes
  - external genitalia
- penetrating trauma
  - damage to: kidney, bladder, ureter (rare), external genitalia
- acceleration/deceleration injury
  - renal pedicle injury: high mortality rate (laceration and thrombosis of renal artery, renal vein, and their branches)
- iatrogenic
  - ureter and urethra (from instrumentation)

### History
- mechanism of injury
- hematuria (microscopic or gross), blood on underwear
- dysuria, urinary retention
- history of hypotension

Gross hematuria suggests bladder injury

### Physical Exam
- abdominal pain, flank pain, CVA tenderness, upper quadrant mass, perineal lacerations
- DRE: sphincter tone, position of prostate, presence of blood
- scrotum: ecchymoses, lacerations, testicular disruption, hematomas
- bimanual exam, speculum exam
- extraperitoneal bladder rupture: pelvic instability, suprapubic tenderness from mass of urine or extravasated blood
- intraperitoneal bladder rupture: acute abdomen
- urethral injury: perineal ecchymosis, scrotal hematoma, blood at penile meatus, high riding prostate, pelvic fractures

### Investigations
- urethra: retrograde urethrography
- bladder: U/A, CT scan, urethrogram ± retrograde cystoscopy ± cystogram (distended bladder + post-void)
- ureter: retrograde ureterogram
- renal: CT scan (best, if hemodynamically stable), intravenous pyelogram

In the case of gross hematuria, the GU system is investigated from distal to proximal (i.e. urethrogram, cystogram, etc.)

### Management
- urology consult
- renal
  - minor injuries: conservative management
    - bedrest, hydration, analgesia, antibiotics
  - major injuries: admit
    - conservative management with frequent reassessments, serial U/A ± re-imaging
    - surgical repair (exploration, nephrectomy): hemodynamically unstable or continuing to bleed >48 h, major urine extravasation, renal pedicle injury, all penetrating wounds and major lacerations, infections, renal artery thrombosis
- ureter
  - ureterouretostomy
- bladder
  - extraperitoneal
    - minor rupture: Foley drainage x 10-14 d
    - major rupture: surgical repair
  - intraperitoneal
- drain abdomen and surgical repair
- urethra
  - anterior: conservative, if cannot void, Foley or suprapubic cystostomy and antibiotics
  - posterior: suprapubic cystostomy (avoid catheterization) ± surgical repair

# Orthopedic Injuries

- see Orthopedic Surgery (see *Shoulder* OR11, *Knee* OR32, *Wrist* OR21, *Ankle* OR38)

### Goals of ED Treatment
- diagnose potentially life/limb threatening injuries
- reduce and immobilize fractures (cast/splint) as appropriate
- provide adequate pain relief
- arrange proper follow-up if necessary

**Description of Fractures**

**SOLARTAT**
**S**ite
**O**pen vs. closed
**L**ength
**A**rticular
**R**otation
**T**ranslation
**A**lignment/Angulation
**T**ype e.g. Salter-Harris, etc.

### History
- use SAMPLE, mechanism of injury may be very important

### Physical Exam
- look (inspection): "SEADS" swelling, erythema, atrophy, deformity, and skin changes (e.g. bruises)
- feel (palpation): all joints/bones for local tenderness, swelling, warmth, crepitus, joint effusions, and subtle deformity
- move: joints affected plus those above and below injury – active ROM preferred to passive
- neurovascular status: distal to injury (before and after reduction)

### LIFE- AND LIMB-THREATENING INJURIES

**Table 10. Life- and Limb-Threatening Orthopedic Injuries**

| **Life-Threatening Injuries** (usually blood loss) | **Limb-Threatening Injuries** (usually interruption of blood supply) |
|---|---|
| Major pelvic fractures | Fracture/dislocation of ankle (talar AVN) |
| Traumatic amputations | Crush injuries |
| Massive long bone injuries and associated fat emboli syndrome | Compartment syndrome |
| Vascular injury proximal to knee/elbow | Open fractures |
| | Dislocations of knee/hip |
| | Fractures above knee/elbow |

### Open Fractures
- communication between fracture site and external surface of skin – increased risk of osteomyelitis
- remove gross debris, irrigate, cover with sterile dressing – formal irrigation and debridement often done in the OR
- control bleeding with pressure (no clamping)
- splint
- antibiotics (1st generation cephalosporin and aminoglycoside) and tetanus prophylaxis
- standard of care is to secure definitive surgical management within 6 h, time to surgery may vary from case-to-case

**When Dealing with an Open Fracture, Remember "STAND"**
**S**plint
**T**etanus prophylaxis
**A**ntibiotics
**N**eurovascular status (before and after)
**D**ressings (to cover wound)

## Vascular Injuries
- realign limb/apply longitudinal traction and reassess pulses (e.g. Doppler probe)
- surgical consult
- direct pressure if external bleeding

## Compartment Syndrome
- when the intracompartmental pressure within an anatomical area (e.g. forearm or lower leg) exceeds the capillary perfusion pressure, eventually leading to muscle/nerve necrosis
- clinical diagnosis: maintain a high index of suspicion
  - pain out of proportion to the injury
  - pain worse with passive stretch
  - tense compartment
  - look for "the 6 Ps" (note: radial pulse pressure is 120/80 mmHg while capillary perfusion pressure is 30 mmHg, seeing any of the 6ps indicates advanced compartment syndrome, therefore do not wait for these signs to diagnose and treat)
- requires prompt decompression: remove constrictive casts, dressings; emergent fasciotomy may be needed

Vascular injury/compartment syndrome is suggested by **"The 6 Ps" Injury**
**Compartment Syndrome - 6 Ps**
**P**ulse discrepancies
**P**allor
**P**aresthesia/hypoesthesia
**P**aralysis
**P**ain (especially when refractory to usual analgesics)
**P**olar (cold)

## UPPER EXTREMITY INJURIES
- anterior shoulder dislocation
  - axillary nerve (lateral aspect of shoulder) and musculocutaneous nerve (extensor aspect of forearm) at risk
  - seen on lateral view: humeral head anterior to glenoid
  - reduce (traction, scapular manipulation), immobilize in internal rotation, repeat x-ray, out-patient follow-up with orthopedics
  - with forceful injury, look for fracture
- Colles' fracture
  - distal radius fracture with dorsal displacement from "Fall on Outstretched Hand" (FOOSH)
  - AP film: shortening, radial deviation, radial displacement
  - lateral film: dorsal displacement, volar angulation
  - reduce, immobilize with splint, out-patient follow-up with orthopedics or immediate orthopedic referral if complicated fracture
  - if involvement of articular surface, emergent orthopedic referral
- scaphoid fracture
  - tenderness in anatomical snuff box, pain on scaphoid tubercle, pain on axial loading of thumb
  - negative x-ray: thumb spica splint, repeat x-ray in 1 wk ± CT scan/bone scan
  - positive x-ray: thumb spica splint x 6-8 wk, repeat x-ray in 2 wk
  - risk of AVN of scaphoid if not immobilized
  - outpatient orthopedics follow-up

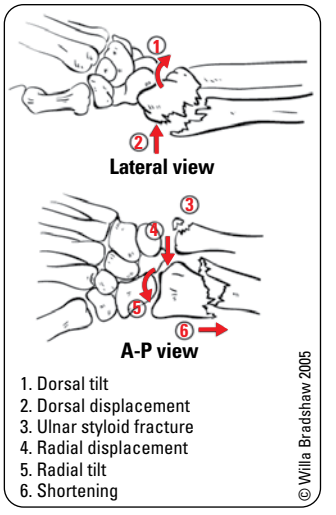



**Figure 7. Colles' fracture**

## LOWER EXTREMITY INJURIES
- ankle and foot fractures
  - see Ottawa Ankle and Foot Rules
- knee injuries
  - see Ottawa Knee Rules
- avulsion of the base of 5th metatarsal
  - occurs with inversion injury
  - supportive tensor or below knee walking cast for 3 wk
- calcaneal fracture
  - associated with fall from height
  - associated with axial loading (other injuries may involve ankles, knees, hips, pelvis, lumbar spine)

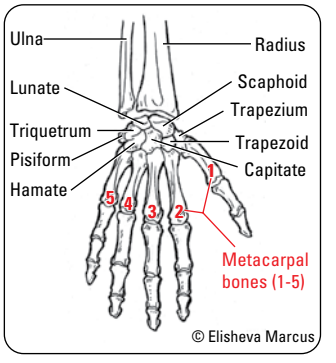
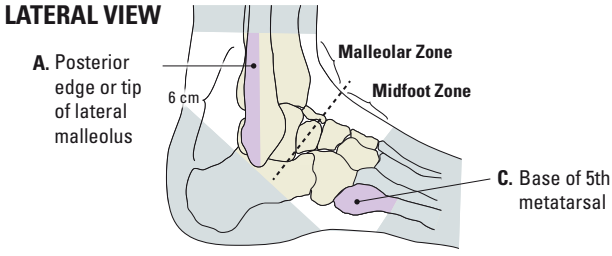
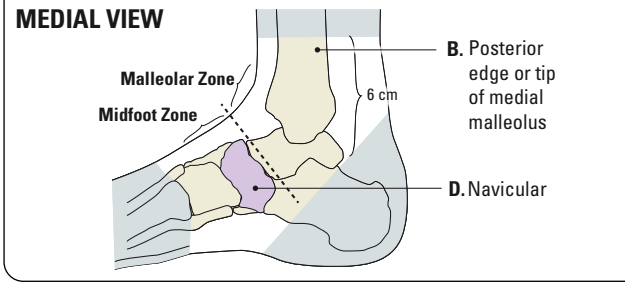



**Figure 8. Carpal bones**

**A knee x-ray examination is required only for acute injury patients with one or more of:**
- Age 55 yr or older
- Tenderness at head of fibula
- Isolated tenderness of patella
- Inability to flex to 90°
- Inability to bear weight both immediately and in the ED (four steps)

**Figure 9. Ottawa knee rules**
Adapted from: Stiell IG, et al. JAMA 1997;278:2075-2079.




An ankle radiographic series is required only if there is any pain in malleolar zone and any of these findings:

1. Bony tenderness at A
or
2. Bony tenderness at B
or
3. Inability to bear weight both immediately and in ED

A radiographic series is required only if there is any pain in midfoot zone and any of these findings:

1. Bony tenderness at C
or
2. Bony tenderness at D
or
3. Inability to bear weight both immediately and in ED

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**Figure 10. Ottawa ankle and foot rules**
Adapted from: Stiell IG, et al. JAMA 1994;271:827-832.

# Wound Management

## Goals of ED Treatment

- identify injuries and stop any active bleeding – direct pressure
- manage pain
- wound examination and exploration (history and physical)
- cleansing ± antibiotic and tetanus prophylaxis
- closure and dressing

## Tetanus Prophylaxis

- both tetanus toxoid (Td) and immunoglobulin (TIG) are safe in pregnancy

**Table 11. Guidelines for Tetanus Prophylaxis for Wounds**

| | Clean, Minor Wounds | | All Other Wounds* | |
|---|---|---|---|---|
| **Vaccination History** | Tdap or Td† | TIG | Tdap or Td† | TIG |
| **Unknown or fewer than 3 doses** | Yes | No | Yes | Yes |
| **3 or more doses** | No§ | No | No¶ | No |

*Such as, but not limited to, wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite
†Tdap is preferred to Td for adults who have never received Tdap. Single antigen tetanus toxoid (TT) is no longer available in the United States
§Yes, if more than ten years since the last tetanus toxoid-containing vaccine dose
¶Yes, if more than five years since the last tetanus toxoid-containing vaccine dose
Source: *MMWR* 1991;40(No. RR-10):1-28

## Bruises

- non-palpable = ecchymosis
- palpable collection (not swelling) = hematoma following blunt trauma
- assess for coagulopathy (e.g. liver disease), anticoagulant use

## Abrasions

- partial to full thickness break in skin
- management
  - clean thoroughly with brush to prevent foreign body impregnation ± local anesthetic antiseptic ointment (Polysporin® or Vaseline®) for 7 d for facial and complex abrasions tetanus prophylaxis

## Lacerations

- see Plastic Surgery, PL23
- consider every structure deep to a laceration injured until proven otherwise
- in hand injury patients, include the following in history: handedness, occupation, mechanism of injury, previous history of injury

**Acute Treatment of Contusions**

**RICE**
**R**est
**I**ce
**C**ompression
**E**levation

**High Risk Factors for Infection**
**Wound Factors**
- Puncture wounds
- Crush injuries
- Wounds >12 h old
- Hand or foot wounds

**Patient Factors**
- Age >50 yr
- Prosthetic joints or valves (risk of endocarditis)
- Immunocompromised

**Suture Use and Duration**

| Suture to: | Close with Nylon or Other Non-absorbable Suture | Approx. Duration (days) |
|---|---|---|
| Face | 6-0 | 5 |
| Not Joint | 4-0 | 7 |
| Joint | 3-0 | 10 |
| Scalp | 4-0 | 7 |
| Mucous Membrane | absorbable (vicryl) | N/A |

N.B. Patients on steroid therapy may need sutures for longer periods of time

- physical exam
  - think about underlying anatomy
  - examine tendon function actively against resistance and neurovascular status distally
  - clean and explore under local anesthetic; look for partial tendon injuries
  - x-ray or U/S wounds if a foreign body is suspected (e.g. shattered glass) and not found when exploring wound (remember: not all foreign bodies are radioopaque), or if suspect intra-articular involvement
- management
  - disinfect skin/use sterile techniques
  - irrigate copiously with normal saline
  - analgesia ± anesthesia
  - maximum dose of lidocaine
    - 7 mg/kg with epinephrine
    - 5 mg/kg without epinephrine
- in children, topical anesthetics such as LET (lidocaine, epinephrine, and tetracaine), and in selected cases a short-acting benzodiazepine (midazolam or other agents) for sedation and amnesia are useful
- secure hemostasis
- evacuate hematomas, debride non-viable tissue, remove hair and foreign bodies
- ± prophylactic antibiotics (consider for animal/human bites, intra-oral lesion, or puncture wounds to the foot)
- suture unless: delayed presentation (>6-8 h), puncture wound, mammalian bite, crush injury, or retained foreign body
- take into account patient and wound factors when considering suturing
- advise patient when to have sutures removed
- cellulitis and necrotizing fasciitis (see Plastic Surgery, PL15)

Early wound irrigation and debridement are the most important factors in decreasing infection risk

**Alternatives to Sutures**
- Tissue glue
- Steristrips®
- Staples

# Approach to Common ED Presentations

## Abdominal Pain

**Table 12. Selected Differential Diagnosis of Abdominal Pain**

| | Emergent | Usually Less Emergent |
|---|---|---|
| **GI** | Perforated viscus, bowel obstruction, ischemic bowel, appendicitis, strangulated hernia, IBD flare, esophageal rupture, peptic ulcer disease | Diverticulitis, gastroenteritis, GERD, esophagitis, gastritis, IBS |
| **Hepatobiliary** | Hepatic/splenic injury, pancreatitis, cholangitis, spontaneous bacterial peritonitis | Biliary colic, cholecystitis, hepatitis |
| **Genital** | Female: Ovarian torsion, PID, ectopic pregnancy<br>Male: Testicular torsion | Female: tubo-ovarian abscess, ovarian cyst, salpingitis, endometriosis<br>Male: epididymitis, prostatitis |
| **Urinary** | Pyelonephritis | Renal colic, cystitis |
| **CVS** | MI, aortic dissection, AAA | Pericarditis |
| **Respirology** | PE, empyema | Pneumonia |
| **Metabolic** | DKA, sickle cell crisis, toxin, Addisonian crisis | Lead poisoning, porphyria |
| **Other** | Significant trauma, acute angle closure glaucoma | Abdominal wall injury, herpes zoster, psychiatric, abscess, hernia, mesenteric adenitis |

Be vigilant: alcoholics, very young or elderly patients, and immunosuppressed patients often present atypically
Old age, pregnancy (T3), and chronic corticosteroid use can blunt peritoneal findings, so have an increased level of suspicion for an intra-abdominal process in these individuals

Unstable patients should not be sent for imaging

- differential can be focused anatomically by location of pain: RUQ, LUQ, RLQ, LLQ, epigastric, periumbilical, diffuse

### History
- pain: OPQRST
- review symptoms from GU, gynecological, GI, respiratory, and CV systems
- abdominal trauma/surgeries, most recent colonoscopy

### Physical Exam
- vitals, abdominal (including DRE, CVA tenderness), pelvic/genital, respiratory, and cardiac exams as indicated by history

### Investigations
- ABCs, do not delay management and consultation if patient unstable
- labs: CBC, electrolytes, glucose, BUN/Cr, U/A ± liver enzymes, LFTs, lipase, β-hCG, ECG, troponins, ± VBG/lactate
- AXR: look for calcifications, free air, gas pattern, air fluid levels
- CXR upright: look for pneumoperitoneum (free air under diaphragm), lung disease
- U/S: biliary tract, ectopic pregnancy, AAA, free fluid
- CT: trauma, AAA, pancreatitis, nephro-/urolithiasis, appendicitis, and diverticulitis

**If elevated AST and ALT**
Think hepatocellular injury
AST > ALT: alcohol-related
ALT > AST: viral, drug, toxin

**If elevated ALP and GGT**
Think biliary tree obstruction

### Management
- NPO, IV, NG tube, analgesics, consider antibiotics and anti-emetics
- growing evidence that small amounts of opioid analgesics improve diagnostic accuracy of physical exam of surgical abdomen
- consult as necessary: general surgery, vascular surgery, gynecology, etc.

### Disposition
- admission: surgical abdomen, workup of significant abnormal findings, need for IV antibiotics or pain control
- discharge: patients with a negative lab and imaging workup who improve clinically during their stay; instruct the patient to return if severe pain, fever, or persistent vomiting develops

## Acute Pelvic Pain

### Etiology
- gynecological
  - ovaries: ruptured ovarian cysts (most common cause of pelvic pain), ovarian abscess, ovarian torsion (rare, 50% will have ovarian mass)
  - fallopian tubes: salpingitis, tubal abscess, hydrosalpinx
  - uterus: leiomyomas (uterine fibroids) – especially with torsion of a pedunculated fibroid or in a pregnant patient (degeneration), PID, endometriosis
  - other: ectopic pregnancy (ruptured/expanding/leaking), spontaneous abortion (threatened or incomplete), endometriosis and dysmenorrhea, sexual or physical abuse
- non-gynecological (see causes of lower abdominal pain above)

**Gynecological Causes of Pelvic Pain**
- Ovarian cyst
- Dysmenorrhea
- Mittelschmerz
- Endometriosis
- Ovarian torsion
- Uterine fibroids/neoplasm
- Adnexal neoplasm
- PID + cervicitis

### History and Physical Exam
- pain: OPQRST
- associated symptoms: vaginal bleeding, discharge, dyspareunia, bowel and/or bladder symptoms
- pregnancy and sexual history
- vitals
- gynecological exam: assess for cervical motion tenderness/"chandelier sign" (suggests PID)
- abdominal exam

### Investigations
- β-hCG for all women of childbearing age
- CBC and differential, electrolytes, glucose, Cr, BUN, G&S, PTT/INR
- urinalysis to rule out urologic causes
- vaginal and cervical swabs for C&S during physical exam
- pelvic and abdominal U/S: evaluate adnexa, thickness of endometrium, pregnancy, free fluid or masses in the pelvis
- Doppler flow studies for ovarian torsion

U/S is the preferred imaging modality in the assessment of acute pelvic pain

### Management
- general: analgesia, determine if admission and consults are needed
- specific:
  - ovarian cysts
    - unruptured or ruptured, and hemodynamically stable: analgesia and follow-up
    - ruptured with significant hemoperitoneum: may require surgery
  - ovarian torsion: surgical detorsion or removal of ovary
  - uncomplicated leiomyomas, endometriosis, and secondary dysmenorrhea can usually be treated on an outpatient basis, discharge with gynecology follow-up
  - PID: broad spectrum antibiotics

### Disposition
- referral: gynecological or obstetrical causes requiring surgical intervention, requiring admission, or oncological in nature
- admission: patients requiring surgery, IV antibiotics/pain management
- discharge: negative workup and resolving symptoms; give clear instructions for appropriate follow-up

## Altered Level of Consciousness

### Definitions
- altered mental status: collective, non-specific term referring to change in cognitive function, behaviour, or attentiveness, including:
  - delirium (see Psychiatry, PS22)
  - dementia (see Psychiatry, PS23)
  - lethargy: state of decreased awareness and alertness (patient may appear wakeful)
  - stupor: unresponsiveness but rousable
  - coma: a sleep-like state, not rousable to consciousness

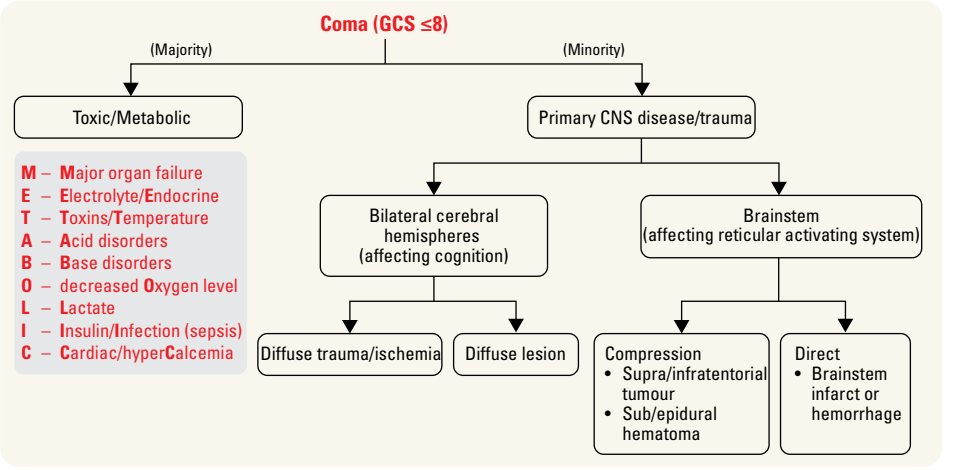



**Figure 11. Etiology of coma**

**Possible Causes of Coma**

**AEIOU TIPS**
**A**cidosis/**A**lcohol
**E**pilepsy
**I**nfection
**O**xygen (hypoxia)/**O**piates
**U**remia
**T**emperature/**T**rauma (especially head)
**I**nsulin (too little or too much)
**P**sychogenic/**P**oisoning
**S**troke

## MANAGEMENT OF ALTERED LOC

### History
- obtain collateral from family, friends, police, paramedics, old chart, MedicAlert® bracelet, etc.
- onset and progression
  - antecedent trauma, seizure activity, fever
  - abrupt onset suggests CNS hemorrhage/ischemia, cardiac cause, or poisoning
  - progression over hours to days suggests progressive CNS lesion or toxic/metabolic cause
- determine patient's baseline LOC
- past medical history (e.g. similar episode(s), depression, overdose)

### Physical Exam
- ABCs, vitals including temperature; cardiac, respiratory, abdominal exams
- complete neurological exam; in particular, examination of the eyes ("PEARL" pupils equal and reactive to light)
  - use the GCS to evaluate LOC (see *Patient Assessment/Management*, ER4)

In general, intubate if GCS <8; but ability to protect airway is primary consideration

### Investigations
- blood work
  - serum glucose level, electrolytes, Cr, BUN, LFTs, serum osmolality, CBC, VBG, PT/PTT/INR, troponins
  - serum acetaminophen, and salicylate levels
- imaging
  - CXR, CT head
- other tests
  - ECG, U/A, UTox

### Diagnosis
- administer appropriate universal antidotes
  - thiamine 100 mg IV if history of EtOH or patient looks malnourished
  - 50 mL D50W if hypoglycemic on finger-prick
  - naloxone 0.4 mg, up to 10 mg IV if opiate overdose suspected
- distinguish between structural and toxic-metabolic coma
  - structural coma
    - pupils, extraocular movements, and motor findings, if present, are usually asymmetric
    - look for focal or lateralizing abnormalities
  - toxic-metabolic coma
    - dysfunction at lower levels of the brainstem (e.g. caloric unresponsiveness)
    - respiratory depression in association with an intact upper brainstem (e.g. equal and reactive pupils; see exceptions in Table 13)
    - extraocular movements and motor findings are symmetric or absent
    - essential to re-examine frequently because status can change rapidly
- diagnosis may become apparent only with the passage of time
  - delayed deficit after head trauma suggestive of epidural hematoma (characteristic "lucid interval")

**Table 13. Toxic-Metabolic Causes of Fixed Pupils**

| Dilated | Dilated to Normal | Constricted |
|---|---|---|
| Anoxia<br>Anticholinergic agents (e.g. atropine, tricyclic antidepressants)<br>Methanol (rare)<br>Cocaine<br>Opioid withdrawal<br>Amphetamines<br>Hallucinogens<br>Serotonin syndrome (MAOI + SSRI) | Hypothermia<br>Barbiturates<br>Antipsychotics | Cholinergic agents (e.g. organophosphates)<br>Opioids (e.g. heroin), except meperidine |

### Disposition
- admission: if ongoing decreased LOC, admit to service based on tentative diagnosis, or transfer patient if appropriate level of care not available
- discharge: readily reversible alteration of LOC; ensure adequate follow-up care available

# Chest Pain

**Table 14. Differential Diagnosis for Chest Pain**

| | Emergent | Usually Less Emergent |
|---|---|---|
| **CVS** | MI, unstable angina, aortic dissection, cardiac tamponade, arrhythmia | Stable angina, pericarditis, myocarditis |
| **Respirology** | PE, pneumothorax | Pneumonia, pleural effusion, malignancy |
| **GI** | Esophageal rupture, pneumomediastinum | Peptic ulcer disease, esophagitis, GERD, esophageal spasm, pancreatitis, cholecystitis |
| **MSK** | | Rib fracture, costochondritis |
| **Other** | | Herpes zoster, psychiatric/panic attack |

**Life-Threatening Causes of Chest Pain**

**PET MAP**
**P**E
**E**sophageal rupture
**T**amponade
**MI**/angina
**A**ortic dissection
**P**neumothorax

### History and Physical Exam
- OPQRST, previous episodes and change in pattern
- cardiac risk factors (HTN, DM, dyslipidemia, smoking, FHx)
- vitals, cardiac, respiratory, peripheral vascular, abdominal exams

Imaging is necessary for all suspected aortic dissections, regardless of BP

### Investigations
- CBC, electrolytes, Cr, BUN, glucose, PTT/INR, cardiac biomarkers (troponins, CK)
- ECG: always compare with previous; may be normal in up to 50% of PE and acute MI
- CXR: compare with previous
- CT: if indicated (e.g. aortic dissection, PE)

**Angina Characteristics**
1. Retrosternal location
2. Provoked by exertion
3. Relieved by rest or nitroglycerin

**Risk for Coronary Artery Disease**
3/3 = "typical angina" - high risk
2/3 = intermediate risk for women >50 yr, all men
1/3 = Intermediate risk in men >40 yr, women >60 yr

### Management and Disposition
- ABCs, $O_2$, cardiac monitors, IV access
- treat underlying cause and involve consultants as necessary
- consider further observation/monitoring if unclear diagnosis or risk of dysrhythmia
- discharge: patients with a low probability of life-threatening illness due to resolving symptoms and negative workup; arrange follow-up and instruct to return if SOB or increased chest pain develops

**Table 15. Comparison of Chest Pain Diagnoses**

| | Classic History | Classic Findings | Diagnostic Investigations | Management and Disposition |
|---|---|---|---|---|
| **Acute Coronary Syndrome** | New or worsening pattern of retrosternal squeezing/pressure pain, radiation to arm/neck, dyspnea, worsened by exercise, relieved by rest; N/V; syncope | New or worsened murmur, hypotension, diaphoresis, pulmonary edema | ECG: ischemia (15-lead if hypotensive, AV node involvement or inferior MI), serial troponin I (sensitive 6-8 h after onset), CK-MB, CXR | ABCs, aspirin, anticoagulation and emergent cardiology consult to consider percutaneous intervention or thrombolytic |
| **Pulmonary Embolism** | Pleuritic chest pain (75%), dyspnea; risk factors for venous thromboembolism | Tachycardia, hypoxemia; evidence of DVT | Wells' criteria: D-dimer, CT pulmonary angiogram*, V/Q scan; leg Doppler, CXR | ABCs, anticoagulation; consider airway management and thrombolysis if respiratory failure |
| **Acute Pericarditis** | Viral prodrome, anterior precordial pain, pleuritic, relieved by sitting up and leaning forward | Triphasic friction rub | ECG: sinus tachycardia, diffuse ST elevation, PR depression in II, III, avF and V4-6; reciprocal PR elevation and ST depression in aVR ±V1; echocardiography | ABCs, rule out MI, high dose NSAIDs ± colchicine; consult if chronic/recurrent or non-viral cause (e.g. SLE, renal failure, requires surgery) |
| **Pneumothorax** | Trauma or spontaneous pleuritic chest pain often in tall, thin, young male athlete | Hemithorax with decreased/absent breath sounds, hyper-resonance; deviated trachea and hemodynamic compromise | Clinical diagnosis CXR: PA, lateral, expiratory views – lung edge, loss of lung markings, tracheal shift; deep sulcus sign on supine view | ABCs, if unstable, needle to 2nd ICS at MCL; urgent surgical consult / thoracostomy 4th ICS and chest tube |
| **Aortic Dissection** | Sudden severe tearing retrosternal or midscapular pain ± focal pain/neurologic loss in extremities in context of HTN | HTN; systolic BP difference >20 mmHg or pulse deficit between arms; aortic regurgitant murmur | CT angio; CXR - wide mediastinum, left pleural effusion, indistinct aortic knob, >4 mm separation of intimal calcification from aortic shadow, 20% normal | ABCs, reduce BP and HR; classify type A (ascending aorta, urgent surgery) vs. B (not ascending aorta, medical) on CT angio and urgent consult |
| **Cardiac Tamponade** | Dyspnea, cold extremities, ± chest pain; often a recent cardiac intervention or symptoms of malignancy, connective tissue disease | Beck's triad - hypotension, elevated JVP, muffled heart sounds; tachycardia, pulsus paradoxus >10 mmHg | Clinical diagnosis CXR: may show cardiomegaly, evidence of trauma | ABCs, cardiac surgery or cardiology consult, pericardiocentesis if unstable, treat underlying cause |
| **Esophageal Rupture** | Sudden onset severe pain after endoscopy, forceful vomiting, labour, or convulsion, or in context of corrosive injury or cancer | Subcutaneous emphysema, findings consistent with sepsis | CXR: pleural effusion (75%), pneumomediastinum; CT or water soluble contrast esophagogram | ABCs, early antibiotics, resuscitation, thoracics consult, NPO, consider chest tube |
| **Esophagitis or GERD** | Frequent heartburn, acid reflux, dysphagia, relief with antacids | Oral thrush or ulcers (rare) | None acutely | ABCs, PPI, avoid EtOH, tobacco, trigger foods |
| **Herpes Zoster** | Abnormal skin sensation – itching/tingling/pain – preceding rash by 1-5 d | None if early; maculopapular rash developing into vesicles and pustules that crust | Clinical diagnosis; direct immunofluorescence assay | ABCs, anti-virals, analgesia ±steroids, dressing; r/o ocular involvement/refer if necessary |
| **MSK** | History of injury | Reproduction of symptoms with movement or palpation (not specific – present in 25% of MI) | MSK injury or fracture on X-rays | ABCs, NSAIDs, rest, orthopedics consultation for fractures |
| **Anxiety** | Symptoms of anxiety, depression, history of psychiatric disorder; may coexist with physical disease | Tachycardia, diaphoresis, tremor | Diagnosis of exclusion | ABCs, arrange social supports, rule out suicidality and consider psychiatry consult |



ACS more likely to be atypical in females, diabetics, and >80 yr. Anginal equivalents include dyspnea, diaphoresis, fatigue, non-retrosternal pain



**Signs of PE on CXR**
**Westermark's sign**: abrupt tapering of a vessel on chest film
**Hampton's hump**: a wedge-shaped infiltrate that abuts the pleura
Effusion, atelectasis, or infiltrates 50% normal



It is important to look for reciprocal changes in STEMI in order to differentiate from pericarditis (diffuse elevations)



Tracheal deviation is away from tension or towards non-tension pneumothorax



**Does this patient with chest pain have acute coronary syndrome?: The rational clinical examination systematic review**
JAMA 2015;314:1955-1965
**Objective**: To review accuracy of the initial history, physical examination, electrocardiogram, and risk scores incorporating these elements with the first cardiac-specific troponin.
**Methods**: Systematic review of prospective studies among patients admitted to emergency department with symptoms suggesting ACS.
**Results**: Prior abnormal stress test (specificity 96%; LR 3.1, 95% CI 2.0-4.7), peripheral artery disease (specificity 97%; LR 2.7, 95% CI 1.5-4.8), and pain radiating to both arms (specificity 96%; LR 2.6, 95% CI 1.8-3.7) were most suggestive of ACS. The most suggestive electrocardiogram findings were ST-segment depression and any evidence of ischemia. The History, Electrocardiogram, Age, Risk Factors, Troponin (HEART) (LR 13, 95% CI 7-24) and the Thrombolysis in Myocardial Infarction (TIMI) risk scores (LR 6.8, 95% CI, 5.2-8.9) were both predictive of ACS in the high-risk scores.
**Conclusions**: Among patients with suspected ACS presenting to emergency departments, the initial history, physical examination, and electrocardiogram alone did not confirm or exclude the diagnosis of ACS. Instead, the HEART or TIMI risk scores, which incorporate the first cardiac troponin, provided more diagnostic information

**Table 16. Common Life-Threatening ECG Changes**

| Pathology | ECG Findings |
|---|---|
| **Dysrhythmia** | |
| Torsades de pointes | Ventricular complexes in upward-pointing and downward-pointing continuum (160-250 bpm) |
| Ventricular tachycardia | 6 or more consecutive premature ventricular beats (>100bpm, QRS >120ms) |
| Ventricular flutter | Smooth sine wave pattern of similar amplitude (>200bpm) |
| Ventricular fibrillation | Erratic ECG tracing, no identifiable waves |
| **Conduction** | |
| 2nd degree heart block (Mobitz Type II) | PR interval stable, some QRSs dropped |
| 3rd degree heart block | Prolonged QRS complex (>0.12 s)<br>RSR' in V5 or V6<br>Total AV dissociation, but stable P-P and R-R intervals |
| Left bundle branch block | Monophasic I and V6<br>May see ST elevation<br>Difficult to interpret, new LBBB is considered STEMI equivalent |
| **Ischemia** | |
| STEMI | ST elevation in leads associated with injured area of heart and reciprocal lead changes (depression) |
| **Metabolic** | |
| Hyperkalemia | Tall T waves |
| Hypokalemia | P wave flattening<br>QRS complex widening and flattening<br>U waves appear<br>Flattened T waves |
| **Digitalis Toxicity** | Gradual downward curve of ST<br>At risk for AV blocks and ventricular irritability |
| **Syndromes** | |
| Brugada | RBBB with ST elevation in V1, V2, and V3<br>Susceptible to deadly dysrhythmias, including VFib |
| Wellens | Marked T wave inversion in V2 and V3<br>Left anterior descending coronary stenosis |
| Long QT syndrome | QT interval longer than ½ of cardiac cycle<br>Predisposed to ventricular dysrhythmias |

**Immediate Treatment of Acute MI**

**BEMOAN**
β-blocker
**E**noxaparin
**M**orphine
**O**xygen
**A**SA
**N**itroglycerin

**Common Therapeutic Approach to Severe Migraine**
- 1 L bolus of NS
- prochlorperazine 10 mg IV
- diphenhydramine 25 mg IV
- ketorolac 30 mg IV
- dexamethasone 10 mg IV
- Other options include haloperidol, metoclopramide, ergotamine, sumatriptan, analgesics

**Ottawa SAH Rule**
JAMA 2013;310(12): 1248-55
- Use for alert patients older than 15 yr with new severe non-traumatic headache reaching maximum intensity within 1 h
- Not for patients with new neurologic deficits, previous aneurysms, SAH, brain tumours, or history of recurrent headaches (≥3 episodes over the course of ≥6 mo)
- Investigate if ≥1 high-risk variables present:
  - Age ≥40 yr
  - Neck pain or stiffness
  - Witnessed loss of consciousness
  - Onset during exertion
  - Thunderclap headache (instantly peaking pain)
  - Limited neck flexion on examination

Subarachnoid hemorrhage can be predicted with 100% sensitivity using this rule.

**Validation of the Ottawa Subarachnoid Hemorrhage Rule in Patients with Acute Headache**
CMAJ 2017;189:E1379-E1385
**Objectives**: Validate the Ottawa SAH Rule in emergency department patients. Methods: Prospective cohort study at 6 university-affiliated tertiary-care hospital emergency departments in Canada from 2010-2014. Included alert, neurologically intact adult patients with headache peaking within 1 hour of onset. The rule was scored before investigations.
**Results**: 1153/1743 potentially eligible patients were enrolled, 67 had subarachnoid hemorrhage. Ottawa SAH rule had 100% sensitivity and 13.6% specificity with similar neuroimaging rates (87%).
**Conclusions**: The Ottawa SAH Rule was sensitive for identifying subarachnoid hemorrhage in otherwise alert and neurologically intact patients.

**Meningitis**
- Do not delay IV antibiotics for LP
- Deliver first dose of dexamethasone with or before first dose of antibiotic therapy

# Headache

- see Neurology, N44

## Etiology

- **common and less serious**
  - common migraine (without aura)/classic migraine (with aura)
    - common: unilateral, throbbing, aggravated by activity, moderate/severe intensity, N/V, photo-/phonophobia
    - classic: fully reversible aura symptoms that precede headache, e.g. flashing lights, pins and needles (paresthesia), loss of vision, dysarthria
    - treatment: simple analgesics (NSAIDs, acetaminophen, aspirin), antiemetics, triptans
    - family doctor to consider prophylactic treatment
  - tension headache
    - bilateral, non-throbbing, not aggravated by routine physical activity, mild-moderate intensity.
    - can last between 30 min to 7 d
    - triggered with stress, sleep deprivation
    - treatment: modify stressor(s), simple analgesics (NSAIDs, acetaminophen, aspirin)
- **less common but potentially fatal**
  - subarachnoid hemorrhage (SAH) (see Neurosurgery, NS18)
    - sudden onset, "worst headache of life," maximum intensity within minutes
    - increased pain with exertion, N/V, meningeal signs
    - diagnosis
      - new generation CT 100% sensitive within 6 h of onset (hyperattentuating signal around Circle of Willis)
      - LP if suspected SAH and normal CT after 6 h
    - management: urgent neurosurgery consult

- increased ICP
  - worse in morning, when supine or bending down, with cough or Valsalva
  - physical exam: neurological deficits, cranial nerve palsies, papilledema
  - diagnosis: CT head
  - management: consult neurosurgery
- meningitis (see Infectious Diseases, ID15)
  - flu-like symptoms (fever, N/V, malaise), meningeal signs, petechial rash
  - altered LOC and confusion
  - rule out increased ICP; if CT head and mental status normal, if no neurological signs and no papilledema, then do LP for diagnosis
  - treatment: early empiric antibiotics ± acyclovir, steroid therapy
- temporal arteritis (causes significant morbidity, blindness) (see Ophthalmology, OP35)
  - vasculitis of large and mid-sized arteries, gender 3:1 F:M, most commonly age >70 yr
  - headache, scalp tenderness, jaw claudication, arthralgia, myalgia, fever, malaise or weight loss
  - temporal artery tender on palpation, relative afferent pupillary defect (RAPD), optic disc edema on fundoscopy
  - labs: elevated ESR, CRP
  - temporal artery biopsy is gold standard for diagnosis
  - associated with polymyalgia rheumatica
  - treatment: high-dose steroids immediately if suspected, no need to hold treatment until pathology results

**Parenteral Dexamethasone for Preventing Recurrence of Acute Severe Migraine Headache**
BMJ 2008;336(7657):1359
**Purpose:** To examine effectiveness of parenteral corticosteroids for relief of acute sevaere migraine headache and prevention of recurrent headaches.
**Methods:** Meta-analysis of RCTs comparing corticosteroids (alone or in combination with standard abortive therapy) to placebo or any other standard treatment for acute migraine in adults.
**Results:** Seven RCTs met eligibility criteria, all of which used standard abortive therapy and subsequently compared single dose parenteral dexamethasone to placebo. All trials examined pain relief and recurrence of headache within 72 hr. While dexamethasone and placebo were comparable for acute pain reduction (mean difference 0.37, 95% CI -0.20 to 0.94) and side effect profiles, dexamethasone provided lower recurrence rates (relative risk 0.75, 0.60 to 0.90; number needed to treat 9).
**Conclusion:** Single dose parenteral dexamethasone with standard abortive therapy is associated with a 26% relative reduction in headache recurrence within 72 h.

### Disposition
- admission: if underlying diagnosis is critical or emergent, if there are abnormal neurological findings, if patient is elderly or immunocompromised (atypical presentation), or if pain is refractory to oral medications
- discharge: assess for risk of narcotic misuse; most patients can be discharged with appropriate analgesia and follow-up with their family physician; instruct patients to return for fever, vomiting, neurologic changes, or increasing pain

## Joint and Back Pain

### JOINT PAIN (see Rheumatology, RH3)
- rule out life threatening causes e.g. septic joint (see Orthopedic Surgery, OR11)

### History and Physical Exam
- history: recent trauma, drug use (anticoagulants, glucocorticoids)
- associated symptoms: fever, constitutional symptoms, skin lesions, conjunctivitis, urethritis
- patterns of joint involvement: polyarticular vs. monoarticular, symmetric vs. asymmetric
- inflammatory symptoms: morning stiffness ≥30 min, pain/stiffness that ease with activity, mid-day fatigue, soft tissue swelling
- non-inflammatory symptoms: morning stiffness <30 min, stiffness short-lived after inactivity, increasing pain with activity
- assess for pain with ROM, localized joint pain, effusion, erythema, warmth, swelling, inability to bear weight, fever; may indicate presence of septic joint

### Investigations
- blood work: CBC, ESR, CRP, WBC, INR/PTT, blood cultures, urate
- joint x-ray ± contralateral joint for comparison
- bedside U/S to identify effusion
- test joint aspirate for: culture, WBC, polynuclear cells, glucose, Gram stain, crystals

### Management
- septic joint: empiric IV antibiotics ± joint decompression and drainage
- crystalline synovitis: NSAIDs at high dose, colchicine within first 24 h, corticosteroids
  - do not use allopurinol, as it may worsen acute attack
- acute polyarthritis: NSAIDs, analgesics (acetaminophen ± opioids), local or systemic corticosteroids
- osteoarthritis: NSAIDs, acetaminophen
- soft tissue pain: allow healing with enforced rest ± immobilization
  - non-pharmacologic treatment: local heat or cold, electrical stimulation, massage
  - pharmacologic: oral analgesics, NSAIDs, muscle relaxants, corticosteroid injections, topical agents

### BACK PAIN (see Family Medicine, FM37)
- rule out extraspinal emergencies: aortic dissection, AAA, PE, MI, retroperitoneal bleed, pancreatitis
- rule out spinal emergencies: osteomyelitis, cauda equina, epidural abscess or hematoma, spinal fracture

### History and Physical Exam
- evaluate risk for fracture (osteoporosis, age), infection (IV drug user, recent spinal intervention, immunosuppression), cancer, vascular causes (cardiac risk factors)
- typical musculoskeletal back pain is moderate, worse with movement or cough with no visceral symptoms
- assess vital signs, perform precordial, abdominal, and neurologic examination of lower extremities

### Investigations
- reserve imaging for suspicion of emergencies, metastases, and patients at high risk of fracture, infection, cancer, or vascular causes
- WBC, ESR, CRP, U/A

### Management
- treat underlying cause
- lumbosacral strain and disc herniation: analgesia and continue daily activities as much as tolerated; discuss red flags and organize follow-up
- spinal infection: early IV antibiotics and ID consultation
- cauda equina: dexamethasone, early neurosurgical consultation

**Red Flags for Back Pain**
**B**owel or bladder dysfunction
**A**nesthesia (saddle)
**C**onstitutional symptoms
**K - C**hronic disease, Constant pain
**P**aresthesia
**A**ge >50 and mild trauma
**I**V drug use/infection
**N**euromotor deficits

## Seizures

- see Neurology, N18

### Definition
- paroxysmal alteration of behaviour and/or EEG changes resulting from abnormal, excessive activity of neurons
- status epilepticus: continuous or intermittent seizure activity for greater than 5 min without regaining consciousness (life threatening)

### Categories
- generalized seizure (consciousness always lost): tonic/clonic, absence, myoclonic, atonic
- partial seizure (focal): simple partial, complex partial
- causes: primary seizure disorder, structural (trauma, intracranial hemorrhage, infection, increased ICP), metabolic disturbance (hypo-/hyperglycemia, hypo-/hypernatremia, hypocalcemia, hypomagnesemia, toxins/drugs)
- differential diagnosis: syncope, stroke/TIA, pseudoseizures, migraines, movement disorders, narcolepsy/cataplexy

### History and Physical Exam
- history of seizures, identify potential precipitants (illness, alcohol use, sleep deprivation)
- preceding aura, rapid onset, brief duration, alterations in consciousness, tonic-clonic movements, and post-ictal symptoms would suggest a seizure
- common signs include loss of bladder/bowel control, tongue biting, emesis and aspiration
- perform vitals, complete neurologic examination and look for injuries to head, spine, and shoulder (dislocations)

**Table 17. Concurrent Investigation and Management of Status Epilepticus**

| Timing | Steps |
|---|---|
| **Immediate** | Protect airway with positioning; intubate if airway compromised or elevated ICP<br>Monitor: vital signs, ECG, oximetry; bedside blood glucose<br>Establish IV access<br>Benzodiazepine - IV lorazepam 2 mg at 2mg/min up to 10 mg or IM midazolam 5mg up to 10mg; repeat at 10 min if ineffective<br>Fluid resuscitation<br>IV dextrose if glucose <60 mg/dL<br>Give 50 mL 50% glucose (preceded by thiamine 100 mg IM in adults)<br>Obtain blood samples for glucose, CBC, electrolytes, $Ca^{2+}$, $Mg^{2+}$, toxins, and antiepileptic drug levels; consider prolactin, β-hCG<br>Vasopressor support if sBP <90 or MAP <70 mmHg |
| **Urgent** | Establish second IV line, urinary catheter<br>If status persists, phenytoin 20 mg/kg IV at 25-50 mg/min in adults; may give additional 10 mg/kg IV 10 min after loading infusion<br>If seizure resolves, antiepileptic drug still required to prevent recurrence<br>EEG monitoring to evaluate for non-convulsive status epilepticus |
| **Refractory** | If status persists after maximum doses above, consult ICU and start one or more of:<br>Phenobarbital 20 mg/kg IV at 50 mg/min<br>Midazolam 0.2 mg/kg IV loading dose and 0.1-0.4 mg/kg/h<br>Propofol 2 mg/kg IV at 2-5 mg/kg/h then loading dose then 2-10 mg/kg/h |
| **Post-Seizure** | Investigate underlying cause: consider CT, LP, MRI, intracranial pressure monitoring |

Note: All interventions should be done as soon as possible
Adapted from Brophy et al. Guidelines for the Evaluation and Management of Status Epilepticus. *Neurocrit Care* 2012;17:3-23

**Minimum Workup in an Adult with 1st Time Seizure**
CBC and differential
Electrolytes including $Ca^{2+}$, $Mg^{2+}$, $PO_4^{3-}$
Head CT

If administering phenytoin, patient must be on a cardiac monitor as dysrhythmias and/or hypotension may occur

If IV access is not feasible, midazolam 0.2 mg/kg IM up to 10 mg can be used for initial control of seizure in adults

### Disposition
- decision to admit or discharge should be based on the underlying disease process identified
  - if a patient has returned to baseline function and is neurologically intact, then consider discharge with outpatient follow-up
- first-time seizure patients being discharged should be referred to a neurologist for follow-up
- admitted patients should generally have a neurology consult
- patient should not drive until medically cleared (local regulations vary)
  - complete notification form to appropriate authority regarding ability to drive
- warn regarding other safety concerns (e.g. no swimming, bathing children alone, etc.)

# Shortness of Breath

- see Respirology, R3 and Cardiology and Cardiac Surgery, C5

**Table 18. Differential Diagnosis for Dyspnea**

| | High Mortality/Morbidity | Usually Less Emergent |
|---|---|---|
| **Respiratory** | Airway obstruction (foreign body, epiglottitis, abscess, anaphylaxis)<br>Pneumo/hemothorax<br>Gas exchange – pulmonary edema, PE, pneumonia,<br>Acute exacerbations of COPD | Chronic obstructive, interstitial or restrictive lung disease<br>Pleural effusion |
| **Cardiac** | CHF, MI, valvular disease, tamponade, arrhythmia | Chronic CHF, angina |
| **Metabolic** | Metabolic acidosis NYD, carbon monoxide inhalation | Anemia, Hemoglobinopathy |
| **Neuromuscular** | Myasthenia gravis, diaphragmatic paralysis | CNS lesion, primary muscle weakness |
| **Other** | | Anxiety, deconditioning |

## History and Physical Exam

- acute SOB is often due to a relatively limited number of conditions; associated symptoms and signs are key to the appropriate diagnosis
  - substernal chest pain with cardiac ischemia
  - fever, cough, and sputum with respiratory infections
  - urticaria with anaphylaxis
  - wheezing with acute bronchospasm
  - environmental or occupational exposures
- dyspnea may be the sole complaint and the physical exam may reveal few abnormalities (e.g. PE, pneumothorax)
- vitals including pulse oximetry
  - wheeze and stridor (airway) vs. crackles (parenchymal), JVP, and murmurs

## Investigations

- blood work
  - CBC and differential (hematocrit to exclude anemia), electrolytes, consider ABG/VBG
  - serial cardiac enzymes and ECG if considering cardiac source
  - Wells scores to consider appropriateness of D-dimer
- imaging
  - CXR (hyperinflation and bullous disease suggestive of obstructive lung disease, or changes in interstitial markings consistent with inflammation, infection, or interstitial fluid)
  - CT chest usually is not indicated in the initial evaluation of patients with dyspnea, but can be valuable in patients with interstitial lung disease, occult emphysema, or chronic thromboembolic disease (i.e. PE)

## Management of Life-Threatening Dyspnea NYD

- see *Primary and Secondary Surveys*, ER2
- treat underlying cause

## Disposition

- the history and physical exam lead to accurate diagnoses in patients with dyspnea in approximately two-thirds of cases; the decision to admit or discharge should be based on the underlying disease process identified
  - consider intubation in $CO_2$ retainers (e.g. COPD)
- if discharging, organize follow-up and educate regarding signs to return to hospital

# Syncope

## Definition

- sudden, transient loss of consciousness and postural tone with spontaneous recovery
- usually caused by generalized cerebral or reticular activating system (brainstem) hypoperfusion

## Etiology

- cardiogenic: dysrhythmia, outflow obstruction (e.g. PE, pulmonary HTN), MI, valvular disease
- non-cardiogenic: peripheral vascular (hypovolemia), vasovagal, cerebrovascular disorders, CNS, metabolic disturbances (e.g. EtOH intoxication)

## History

- gather details from witnesses, and clarify patient's experience (e.g. dizziness, ataxia, or true syncope)
  - two key historical features: prodrome and situation (setting, patient posture)
- distinguish between syncope and seizure (see Neurology, N19)

  - some patients may have myoclonic jerks with syncope – NOT a seizure
    - signs and symptoms during presyncope, syncope, and postsyncope
    - past medical history, drugs
    - think anatomically in differential; pump (heart), blood, vessels, brain
- syncope is cardiogenic until proven otherwise if
  - there is sudden loss of consciousness with no warning or prodrome
  - syncope is accompanied by chest pain

### Physical Exam
- postural BP and HR
- cardiac, respiratory, and neurological exams
- examine for signs of secondary injury caused by syncopal episode (e.g. head injury)

### Investigations
- ECG (tachycardia, bradycardia, blocks, Wolff-Parkinson White, long QT interval, Brugada Syndrome, RV strain), bedside glucose
- consider blood work: CBC, electrolytes, BUN/Cr, ABGs, troponin, $Ca^{2+}$, $Mg^{2+}$, β-hCG, D-dimer
- consider toxicology screen

### Management
- ABCs, IV, $O_2$, monitor
- cardiogenic syncope: admit to medicine/cardiology
- low risk syncope: discharge with follow-up as indicated by cause (non-cardiogenic syncope may still be admitted)

### Disposition
- decision to admit is based on etiology
- most patients will be discharged
- on discharge, instruct patient to follow-up with family physician
  - educate about avoiding orthostatic or situational syncope
  - evaluate the patient for fitness to drive or work
  - patients with recurrent syncope should avoid high-risk activities (e.g. driving)

**Causes of Syncope by System**

**HEAD, HEART, VeSSELS**
**H**ypoxia/Hypoglycemia
**E**pilepsy
**A**nxiety
**D**ysfunctional brainstem
**H**eart attack
**E**mbolism (PE)
**A**ortic obstruction
**R**hythm disturbance
**T**achycardia
**V**asovagal
**S**ituational
**S**ubclavian steal
**E**NT (glossopharyngeal neuralgia)
**L**ow systemic vascular resistance
**S**ensitive carotid sinus

**San Francisco Syncope Rule: High risk of adverse outcomes in syncope patients if:**

**CHESS**
**C**HF: Hx of CHF
**H**ct: Low
**E**CG: Abnormal
**S**OB: Hx of dyspnea
**S**BP: sBP <90 at triage

# Sexual Assault

### Epidemiology
- 1 in 5 women and 1 in 71 men will be sexually assaulted in their lifetime; only 7% are reported

### General Approach
- ABCs, treat acute, serious injuries; physician priority is to treat medical issues and provide clearance
- ensure patient is not left alone and provide ongoing emotional support
- obtain consent for medical exam and treatment, collection of evidence, disclosure to police (notify police as soon as consent obtained)
- Sexual Assault Kit (document injuries, collect evidence) if <72 h since assault
- label samples immediately and pass directly to police
- offer community crisis resources (e.g. shelter, hotline)
- do not report unless victim requests or if <16 yr old (legally required)

### History
- ensure privacy for the patient – others should be asked to leave
- questions to ask: who, when, where did penetration occur, what happened, any weapons, or physical assault?
- post-assault activities (urination, defecation, change of clothes, shower, douche, etc.)
- gynecologic history
  - gravidity, parity, last menstrual period
  - contraception use
  - last voluntary intercourse (sperm motile 6-12 h in vagina, 5 d in cervix)
- medical history: acute injury/illness, chronic diseases, psychiatric history, medications, allergies, etc.

### Physical Exam
- never re-traumatize a patient with the examination
- general examination
  - mental status
  - sexual maturity
  - patient should remove clothes and place in paper bag
  - document abrasions, bruises, lacerations, torn frenulum/broken teeth (indicates oral penetration)

Interprofessional teams are key; many centres or regions have sexual assault teams who specialize in the assessment and treatment of sexual assault victims, leaving emergency physicians responsible only for significant injuries and medical clearance

- pelvic exam and specimen collection
  - ideally before urination or defecation
  - examine for seminal stains, hymen, signs of trauma
  - collect moistened swabs of dried seminal stains
  - pubic hair combings and cuttings
  - speculum exam
    - lubricate with water only
    - vaginal lacerations, foreign bodies
    - Pap smear, oral/cervical/rectal culture for gonorrhea and chlamydia
    - posterior fornix secretions if present or aspiration of saline irrigation
    - immediate wet smear for motile sperm
    - air-dried slides for immotile sperm, acid phosphatase, ABO group
- fingernail scrapings and saliva sample from victim

### Investigations
- Venereal Disease Research Lab (VDRL): repeat in 3 mo if negative
- serum β-hCG
- blood for ABO group, Rh type, baseline serology (e.g. hepatitis, HIV)

### Management
- involve local/regional sexual assault team (sexual assault forensic examiner or sexual assault nurse examiner)
- medical
  - suture lacerations, tetanus prophylaxis
  - gynecology consult for foreign body, complex lacerations
  - assume positive for gonorrhea and chlamydia
    - management: azithromycin 1 g PO x 1 dose (alt: doxycycline 100 mg PO bid x 10 d) and ceftriaxone 250 mg IM x 1 dose
  - may start prophylaxis for hepatitis B and HIV
  - pre and post counselling for HIV testing
  - pregnancy prophylaxis offered
    - levonorgestrel 1.5 g PO STAT (Plan B®)
- psychological
  - high incidence of psychological sequelae
  - have victim change and shower after exam completed

### Disposition
- discharge if injuries/social situation permit
- follow-up with physician in rape crisis centre within 24 h for repeat pregnancy and STI testing.
- best if patient does not leave ED alone

## DOMESTIC VIOLENCE
- women are usually the victims, but male victimization also occurs
- identify the problem (need high index of suspicion)
  - suggestive injuries (bruises, sprains, abrasions, occasionally fractures, burns, or other injuries; often inconsistent with history provided)
  - somatic symptoms (chronic and vague complaints)
  - psychosocial symptoms
  - clinician impression (your 'gut feeling', e.g. overbearing partner that won't leave patient's side)
- if disclosed, be supportive and assess danger
- patient must consent to follow-up investigation/reporting (unless for children)

### Management
- treat injuries and document findings
- ask about sexual assault and children at home (encourage notification of police)
- safety plan with good follow-up with family physician/social worker

# Medical Emergencies

## Anaphylaxis and Allergic Reactions

### Etiology
- anaphylaxis is an exaggerated immune mediated hypersensitivity reaction that leads to systemic histamine release, increased vascular permeability, and vasodilation; regardless of the etiology, the presentation and management of anaphylactic reactions are the same
- allergic (re-exposure to allergen)
- non-allergic (e.g. exercise induced)

**Most Common Triggers for Anaphylaxis**
- Foods (nuts, shellfish, etc.)
- Stings
- Drugs (penicillin, NSAIDs, ACEI)
- Radiographic contrast media
- Blood products
- Latex

### Diagnostic Criteria
- anaphylaxis is highly likely with any of:
  1. acute onset of an illness (min to hrs) with involvement of the skin, mucosal tissue and at least one of
     - respiratory compromise (e.g. dyspnea, wheeze, stridor, hypoxemia)
     - hypotension/end-organ dysfunction (e.g. hypotonia, collapse, syncope, incontinence)
  2. two or more of the following after exposure to a LIKELY allergen for that patient (min to hrs)
     - involvement of the skin-mucosal tissue
     - respiratory compromise
     - hypotension or associated symptoms
     - persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)
  3. hypotension after exposure to a KNOWN allergen for that patient (min to h)
     - management is also appropriate in cases which do not fulfill criteria, but who have had previous episodes of anaphylaxis
     - life-threatening differentials for anaphylaxis include asthma and septic shock
     - angioedema may mimic anaphylaxis but tends not to improve with standard anaphylaxis treatment

Anaphylaxis should be suspected if airway, breathing, or especially circulation compromise is present after exposure to a known allergen

Hypotension is defined as systolic BP >30% decrease from baseline or
- ≥11 yr: <90 mmHg
- 1-10 yr: <70 mmHg + (2 x age)
- 1 mo-1 yr: <70 mmHg

### Management
- moderate reaction: generalized urticaria, angioedema, wheezing, tachycardia
  - epinephrine (1:1000) 0.3-0.5 mg (IM in anterolateral thigh)
  - antihistamines: diphenhydramine (Benadryl®) 25-50 mg PO/IV
  - salbutamol (Ventolin®) 1 cc via MDI
- severe reaction/evolution: severe wheezing, laryngeal/pulmonary edema, shock
  - ABCs, may need definitive airway (e.g. ETT) due to airway edema
  - epinephrine (1:1000) 1-10 µg/min IV (or via ETT if no IV access) titrated to desired effect
  - antihistamines: diphenhydramine (Benadryl®) 50 mg IV (~1 mg/kg)
  - glucocorticoids: methylprednisolone 125-250 mg IV or prednisone/prednisolone 40-60 mg PO
  - large volumes of crystalloid may be required

Early epinephrine is lifesaving and there are no absolute contraindications

**Pediatric Dosing**
- Epinephrine: 0.01 mg/kg IM up to 0.5mg q5-10min
- Initial crystalloid bolus: 20-30 mL/kg, reassess
- Epinephrine infusion: 0.1-1.5 µg/kg/min
- Diphenhydramine: 1 mg/kg PO/IV q4-6h
- Ranitidine: 1 mg/kg PO/IV
- Methylprednisolone: 1-2 mg/kg IV

### Disposition
- monitor for 4-8 h in ED (minimum) and arrange follow-up with family physician in 24-48 h
- can have second phase (biphasic) reaction up to 72 h later, patient may need to be supervised
- educate patient on avoidance of allergens
- medications
  - H1 antagonist (cetirizine 10 mg PO OD or Benadryl® 50 mg PO q4-6h x3d)
  - H2 antagonist (ranitidine 150 mg PO OD x3d)
  - corticosteroid (prednisone 50 mg PO OD x5d) to prevent secondary reaction

## Asthma

- see Respirology, R7
- chronic inflammatory airway disease with episodes of bronchospasm and inflammation resulting in reversible airflow obstruction

### History and Physical
- find cause(s) of asthma exacerbation (viral, environmental, etc.)
- history of asthma control; severity of exacerbations (ICU, intubation history)
- signs of respiratory distress
- vitals, specifically $O_2$

### Investigations
- peak flow metre
- ± ABG if in severe respiratory distress
- CXR if diagnosis in doubt to rule out pneumonia, pneumothorax, etc.

Beware of the silent chest in asthma exacerbations. This is a medical emergency and may require emergency intubation

**Elements of Well-Controlled Asthma**
Can Respir J 2010;17(1):15-24
- Daytime symptoms <4x/wk
- Nocturnal symptoms <1x/wk
- No limitation in activity
- No absence from work/school
- Rescue inhaler use <4x/wk
- $FEV_1$ <90% personal best
- PEF <10-15% diurnal variation
- Mild infrequent exacerbations

**Table 19. Asthma Assessment and Management**

| Classifications | History and Physical Exam | Management |
|---|---|---|
| **Respiratory Arrest Imminent** | Exhausted, confused, diaphoretic, cyanotic<br>Silent chest, ineffective respiratory effort<br>Decreased HR, RR>30, $pCO_2$>45 mmHg<br>$O_2$ sat <90% despite supplemental $O_2$ | 100% $O_2$, cardiac monitor, IV access<br>Intubate (consider induction with ketamine)<br>Short acting β-agonist (Ventolin®): nebulizer 5 mg continually<br>Short-acting anticholinergic (Atrovent®): nebulizer 0.5 mg x 3<br>IV steroids: methylprednisolone 125 mg |
| **Severe Asthma** | Agitated, diaphoretic, laboured respirations<br>Speaking in words<br>No relief from β-agonist<br>$O_2$ sat <90%, $FEV_1$ <50% | Anticipate need for intubation<br>Similar to above management<br>Magnesium sulphate 2 g IV<br>$O_2$ to achieve $O_2$ sat >92% |
| **Moderate Asthma** | SOB at rest, cough, congestion, chest tightness<br>Speaking in phrases<br>Inadequate relief from β-agonist<br>$FEV_1$ 50-80% | $O_2$ to achieve $O_2$ sat >92%<br>Short-acting β-agonist (Ventolin®): MDI or nebulizer q5min<br>Short-acting Anticholinergic (Atrovent®): MDI or nebs x 3<br>Steroids: prednisone 40-60 mg PO |
| **Mild Asthma** | Exertional SOB/cough with some nocturnal symptoms<br>Difficulty finishing sentences<br>$FEV_1$ >80% | β-agonist<br>Monitor $FEV_1$<br>Consider steroids (MDI or PO) |

### Disposition

- discharge safe in patients with $FEV_1$ or PEF >60% predicted, and may be safe if $FEV_1$ or PEF 40-60% predicted based on patient's risk factors for recurrence of severe attack
  - risk factors for recurrence: frequent ED visits, frequent hospitalizations, recent steroid use, recent exacerbation, poor medication compliance, prolonged use of high dose β-agonists
- β-agonist MDI with aerochamber 2-4 puffs q2-4h until symptoms controlled, then prn
- initiate inhaled corticosteroids with aerochamber if not already prescribed
- if moderate to severe attack, administer prednisone 30-60 mg/d for 5-10 d with no taper
- counsel on medication adherence and educate on use of aerochamber
  - follow-up with primary care physician or asthma specialist

**Combined Inhaled Beta-Agonist and Anticholinergic Agents for Emergency Management in Adults with Asthma**
Cochrane DB Syst Rev 2017:CD001284
**Objectives**: Determine the effectiveness of combined SAAC + SABA inhaled therapy vs. SABA alone to reduce hospitalization in adult patients presenting to emergency department with an exacerbation of asthma.
**Methods**: Systematic review of RCTs.
**Results**: 23 trials, 2724 patients. Combination inhaled therapy was associated with reduced likelihood of hospitalization (RR 0.72, 95% CI 0.59-0.87) for severe but not mild or moderate asthma exacerbations. Combination therapy was also associated with improved FEV1 (MD 0.25L, 95% CI 0.02-0.48) and PEF (MD 24.88, 95% CI 14.83-34.93) and patients were less likely to return to ED for additional care (RR 0.80, 95% CI 0.66-0.98). In contrast, patients receiving combination therapy were more likely to experience adverse events than those treated with SABA alone (OR 2.03, 95% CI 1.28-3.20).
**Conclusions**: Combination SAAC + SABA therapy reduces hospitalizations and improves pulmonary function in adults presenting to the emergency department with acute asthma. However, adults receiving combination therapy were more likely experience adverse events, such as tremor, agitation, and palpitations, compared to patients receiving SABA alone.

# Cardiac Dysrhythmias

- see Cardiology and Cardiac Surgery, C18

### Bradydysrhythmias and AV Conduction Blocks

- AV conduction blocks
  - 1st degree: prolonged PR interval (>200 msec), no treatment required
  - 2nd degree
    - Mobitz I: gradual prolongation of PR interval then dropped QRS complex, usually benign
    - Mobitz II: PR interval constant with dropped QRS complex, can progress to 3rd degree AV block
  - 3rd degree: P wave unrelated to QRS complex, PP and RR intervals constant
    - atropine and transcutaneous pacing (atropine with caution)
    - if transcutaneous pacing fails consider IV dopamine, epinephrine
  - long-term treatment for Mobitz II and 3rd degree block – internal pacemaker
- sinus bradycardia (rate <60 bpm)
  - can be normal (especially in athletes)
  - causes: vagal stimulation, vomiting, myocardial infarction/ischemia, increased ICP, sick sinus node, hypothyroidism, drugs (e.g. β-blockers, calcium channel blockers)
  - treat if symptomatic (hypotension, chest pain)
    - acute: atropine ± transcutaneous pacing
    - sick sinus: transcutaneous pacing
    - drug induced: discontinue/reduce offending drug, consider antidotes

**Adenosine Versus Intravenous Calcium Channel Antagonists For Supraventricular Tachycardia**
Cochrane DB Syst Rev 2017: CD005154
**Objectives**: Compare adenosine versus calcium channel antagonists in terminating supraventricular tachycardia.
**Methods**: Systematic review of RCTs for any patient presenting with an supraventricular tachycardia.
**Results**: 7 RCTs, 622 participants. Moderate-quality evidence shows no differences in the number or people reverting to sinus rhythm who were treated with adenosine or calcium channel antagonist (89.7% vs. 92.9%, OR 1.51). Low-quality evidence suggests no differences in major adverse event rates.
Conclusions: Moderate-quality evidence shows no differences in effects of adenosine and calcium channel antagonists for treatment of supraventricular tachycardia on reverting to sinus rhythm, and low-quality evidence suggests no differences in the incidence of hypotension

### Supraventricular Tachydysrhythmias (narrow QRS)

- sinus tachycardia (rate >100 bpm)
  - causes: increased sympathetic tone, drugs, fever, hypotension, anemia, thyrotoxicosis, MI, PE, emotional, pain, etc.
  - search for and treat underlying cause, consider β-blocker if symptomatic
- regular rhythm (i.e. not sinus tachycardia)
  - vagal maneuvers (carotid massage, Valsalva), adenosine 6 mg IV push, if no conversion give 12 mg, can repeat 12 mg dose once
  - rhythm converts: probable re-entry tachycardia (AVNRT more common than AVRT)
    - monitor for recurrence
    - treat recurrence with adenosine or longer acting medications
  - rhythm does not convert: atrial flutter, ectopic atrial tachycardia, junctional tachycardia
    - rate control (diltiazem, β-blockers) and consult cardiology
- irregular rhythm
  - probable AFib, atrial flutter, or multifocal atrial tachycardia
  - rate control (diltiazem, β-blockers)

If the patient with tachydysrhythmia is unstable, perform immediate synchronized cardioversion

### Atrial Fibrillation

- most common sustained dysrhythmia; no organized P waves (atrial rate >300/min), irregularly irregular heart rate, narrow QRS (typically)
- etiology: HTN, CAD, thyrotoxicosis, EtOH (holiday heart), valvular disease, pericarditis, cardiomyopathy, sick sinus syndrome
- treatment principles: stroke prevention, treat symptoms, identify/treat underlying cause
- decreases cardiac output by 20-30% (due to loss of organized atrial contractions)
- acute management
  - if unstable: immediate synchronized cardioversion
  - if onset of AFib is >48 h: rate control, anticoagulate 3 wk prior to and 4 wk after cardioversion, or do transesophageal echocardiogram to rule out clot
  - if onset <48 h or already anticoagulated: may cardiovert
- electrical cardioversion: synchronized direct current (DC) cardioversion
- chemical cardioversion: procainamide, flecainide, propafenone
- long-term management: rate or rhythm control, consider anticoagulation (see Cardiology and Cardiac Surgery, *CHADS2 score* C20)

If patient has Wolff-Parkinson-White and is in AFib use amiodarone or procainamide; avoid AV nodal blocking agents (adenosine, digoxin, diltiazem, verapamil, β-blockers), as this can increase conduction through bypass tract, leading to cardiac arrest

**Causes of Atrial Fibrillation**

**C ("sea") PIRATES**
**C**HF, Cardiomyopathy
**P**ulmonary embolism
**I**schemic heart disease
**R**heumatic or valvular disease
**A**nemia
**T**hyroid
**E**tOH, Elevated blood pressure
**S**ick Sinus, Stress - surgery, sepsis

### Ventricular Tachydysrhythmias (wide QRS)

- VTach (rate usually 140-200 bpm)
  - definition: 3 or more consecutive ventricular beats at >100 bpm
  - etiology: CAD with MI is most common cause
  - treatment: sustained VTach (>30 s) is an emergency
    - hemodynamic compromise: synchronized DC cardioversion
    - no hemodynamic compromise: synchronized DC cardioversion, amiodarone, procainamide
- VFib: call a code blue, follow ACLS for pulseless arrest
- Torsades de pointes
  - looks like VTach but QRS 'rotates around baseline' with changing axis and amplitude (twisted ribbon)
  - etiology: prolonged QT due to drugs (e.g. quinidine, TCAs, erythromycin, quinolones), electrolyte imbalance (hypokalemia, hypomagnesemia), congenital
  - treatment
    - IV $Mg^{2+}$, temporary overdrive pacing, isoproterenol
    - correct cause of prolonged QT

## Acute Exacerbation of COPD (AECOPD)

- see Respirology, *Chronic Management of COPD* R9
- progressive development of irreversible airway obstruction, typically caused by smoking

### History and Physical Exam

- cardinal symptoms of AECOPD: increased dyspnea, increased coughing frequency or severity, increased sputum volume or purulence
- triggers: virus, pneumonia, urinary tract infection, PE, CHF, MI, drugs
- characterize previous episodes and hospitalizations, smoking history
- vital signs, LOC, signs of respiratory distress, respiratory exam

**Physical Exam Findings in COPD**
- Wheeze
- Maximum laryngeal height ≤4 cm
- Forced expiratory time ≥6 s
- Decreased breath sounds
- Decreased cardiac dullness

### Investigations

- CBC, electrolytes, CXR, ECG, consider ABG
- PFTs are NOT useful in managing acute exacerbations

**Need to Rule Out with COPD Exacerbation**
- Pneumothorax
- CHF exacerbation
- Acute MI
- Pneumonia and other infectious causes
- PE

### Management

- oxygen: keep $O_2$ sat 88-92% (be aware when giving $O_2$ to chronic hypercapnic/$CO_2$ retainers but do not withhold $O_2$ if hypoxic)
- bronchodilators: short-acting β-agonist (salbutamol 4-8 puffs via MDI with spacer q15min x3 prn) ± short-acting anticholinergic (ipratropium 0.5 mg via MDI q30min x3 prn)
- steroids: prednisone 40-60 mg PO for 7-14 d, or methylprednisolone 1-2 mg/kg IV if severe exacerbation, or unable to take PO
- antibiotics: TMP-SMX, cephalosporins, respiratory quinolones (given if all 3 cardinal symptoms present or 2 cardinal symptoms with increased sputum purulence or mechanical ventilation)
- ventilation: apply noninvasive positive-pressure ventilation (CPAP or BiPAP) if severe distress or signs of fatigue, arterial pH <7.35, or hypercapnic
- if life-threatening, ICU admission for intubation and ventilation (chance of ventilation dependency)

### Disposition

- no guidelines for admission - based on clinical judgement and comorbidities
- lower threshold to admit if comorbid illness (diabetes, CHF, CAD, alcohol abuse)
- if discharging, use antibiotics, taper steroids, up to 4-6 puffs qid of ipratropium and salbutamol and organize follow-up

# Acute Decompensated Heart Failure (ADHF)

- see Cardiology and Cardiac Surgery, C34

## Etiology

- causes of CHF: decreased myocardial contractility (ischemia, infarction, cardiomyopathy, myocarditis), pressure overload states (HTN, valve abnormalities, congenital heart disease), restricted cardiac output (myocardial infiltrative disease, cardiac tamponade)
- precipitants of acute decompensation of CHF
  - cardiac (ischemia, infarction, arrhythmia - Afib)
  - medications (β-blockers, CCBs, NSAIDs, steroids, non-compliance)
  - dietary (increased sodium and/or water intake)
  - high output (anemia, infection, pregnancy, hyperthyroid)
  - other (renal failure, hypertensive crisis, iatrogenic fluid overload - blood transfusions or IV fluids)

## Presentation

- left-sided heart failure
  - dyspnea, SOBOE, orthopnea, PND, nocturia, fatigue, altered mental status, presyncope/syncope, angina, systemic hypotension
  - hypoxia, decreased air entry to lungs, crackles, S3 or S4, pulmonary edema (on CXR), pleural effusion (usually right-sided)
- right-sided heart failure
  - dependent bilateral pitting edema, JVP elevation and positive AJR, ascites, hepatomegaly
- patients often present with a combination of right-sided and left-sided symptoms

## Investigations

- blood work: CBC, electrolytes, AST, ALT, bilirubin, Cr, BUN, cardiac enzymes, brain natriuretic peptide
- CXR: most useful test (see sidebar)
- ECG: look for MI, ischemia (ST elevation/depression, T-wave inversion), LVH, atrial enlargement, conduction abnormalities
- bedside ultrasound: wall motion abnormalities, ejection fraction, rule out cardiac tamponade
- echocardiogram: LV function, structural heart disease
- rule out other serious diagnoses: PE, pneumothorax, pneumonia/empyema, acute exacerbations COPD

## Management

- ABCs, may require intubation if severe hypoxia
- sit upright, cardiac monitoring, and continuous pulse oximetry
- saline lock IV, Foley catheter due to diuretic therapy
- 100% $O_2$ by mask
  - if poor response, may require BiPAP or intubation
- medical
  - diuretic (if volume overloaded): furosemide 0.5-1 mg/kg IV
  - vasodilators (if sBP >100): nitroglycerin 0.4 mg SL q5min prn ± topical Nitrodur® patch (0.4-0.8 mg/h)
    - if patient not responding to treatment or showing signs of ischemia (angina): nitroglycerine 5-10 µg/min IV, titrate to response
  - inotropes/vasopressors (if sBP <90)
    - without signs of shock: dobutamine 2.5 µg/kg/min IV, titrate up to sBP >90 mmHg
    - with signs of shock: norepinephrine 8-12 µg/min, titrate up to sBP >90 mmHg
- treat precipitating factor - e.g. rate control (β-blocker, calcium channel blockers) or rhythm-control (electrical or chemical cardioversion) if new Afib
- cardiology or medicine consult

**Precipitants of CHF Exacerbation**

**FAILURE**
**F**orgot medication
**A**rrhythmia (Dysrhythmia)/**A**nemia
**I**schemia/**I**nfarction/**I**nfection
**L**ifestyle (e.g. high salt intake)
**U**pregulation of cardiac output (pregnancy, hyperthyroidism)
**R**enal failure
**E**mbolism (pulmonary)

**CHF on CXR**
- Pulmonary vascular redistribution
- Perihilar infiltrates
- Interstitial edema, Kerley B lines
- Alveolar edema, bilateral infiltrates
- May see cardiomegaly, pleural effusions
- Peribronchial cuffing
- Fissural thickening (fluid in fissure)

**Acute Treatment of CHF**

**LMNOP**
**L**asix® (furosemide)
**M**orphine
**N**itroglycerin
**O**xygen
**P**osition (sit upright), **P**ressure (BiPAP)

**Hospital Management Required if**
- Acute MI
- Pulmonary edema or severe respiratory distress
- Severe complicating medical illness (e.g. pneumonia)
- Anasarca
- Symptomatic hypotension or syncope
- Refractory to outpatient therapy
- Thromboembolic complications requiring interventions
- Clinically significant dysrhythmias
- Inadequate social support for safe outpatient management
- Persistent hypoxia requiring supplemental oxygen

# Venous Thromboembolism (VTE)

• see Respirology, R19

## Risk Factors

- Virchow's triad: alterations in blood flow (venous stasis), injury to endothelium (smoking, HTN, surgery, catheter, trauma), hypercoagulable state (including pregnancy, use of OCP, malignancy)
- clinical risk factors (see sidebar)

## DEEP VEIN THROMBOSIS (DVT)

### Presentation

- calf pain, unilateral leg swelling/erythema/edema, palpable cord along the deep venous system on exam; can be asymptomatic
- clinical signs/symptoms are unreliable for diagnosis and exclusion of DVT; investigation often needed

### Investigations

- use Wells' criteria for DVT to guide investigations (see Figure 12)
- D-dimer is only useful for ruling out DVT, and a D-dimer test result should only be considered in cases where a low-moderate risk patient has a negative test (high sensitivity)
  - high risk of false positives in: elderly, infection, recent surgery, trauma, hemorrhage, late in pregnancy, liver disease, cancer
- U/S has high sensitivity & specificity for proximal clot but only 73% sensitivity for calf DVT (may need to repeat in 1 wk)
  - if positive – treat for DVT regardless of risk
  - if negative and low risk – rule out DVT
  - if negative and moderate to high risk – repeat U/S in 5-7 d to rule out DVT

### Management

- DOAC can be used in acute management of symptomatic DVT
  - rivaroxaban: 15 mg PO bid for first 21 d; 20 mg PO daily for remaining treatment (taken with food at the same time each day)
  - apixaban: 10 mg PO bid for first 7 d; 5 mg PO bid for remaining treatment
- LMWH unless patient also has renal failure
  - dalteparin 200 IU/kg SC q24h or enoxaparin 1 mg/kg SC q24h
- warfarin started at same time as LMWH (5 mg PO OD initially followed by dosing based on INR)
- LMWH discontinued when INR has been therapeutic (2-3) for 2 consecutive days
- consider thrombolysis if extensive DVT threatening limb compromise
- IVC filter or surgical thrombectomy considered if anticoagulation is contraindicated
- duration of anticoagulation: 3 mo if transient coagulopathy; 6 mo if unprovoked DVT; life-long if ongoing coagulopathy

## PULMONARY EMBOLISM (PE)

### Presentation

- dyspnea, pleuritic chest pain, hemoptysis, tachypnea, cyanosis, hypoxia, fever
- clinical signs/symptoms are unreliable for diagnosis and exclusion of DVT; investigation often needed

### Investigations

- use Wells' criteria for PE to guide investigations (see Figure 13)
- PERC score alone can rule out PE in low risk patients (as determined by Wells' criteria) unless patient is pregnant
- ECG and CXR are useful to rule out other causes (e.g. ACS, pneumonia, pericarditis) or to support diagnosis of PE
  - ECG changes in PE: sinus tachycardia, right ventricular strain (S1Q3T3), T wave inversions in anterior and inferior leads
  - CXR findings in PE: Hampton's hump (triangular density extending from pleura) or Westermark's sign (dilatation of vessels proximal to an obstruction, with collapse of vessels distal to obstruction, often with a sharp cutoff)
- D-dimer is only useful at ruling out a PE if it is negative in low-moderate risk patients (highly sensitive)
  - if positive D-dimer or high-probability patient, then pursue CT angiography or V/Q scan
- CT angiography has high sensitivity and specificity for PE, may also indicate an alternative diagnosis
- V/Q scan useful in pregnancy, when CT angiography not available, or IV contrast contraindicated

### Management of PE

- treatment of PE with anticoagulation and duration of treatment is the same as for DVT (see above)
- consider thrombolysis if extensive PE causing hemodynamic compromise or cardiogenic shock
- catheter-directed thrombolysis or surgical thrombectomy may be considered in massive PE or if anticoagulation is contraindicated
- often can be treated as outpatient, may require analgesia for chest pain (narcotic or NSAID)

**Risk Factors for VTE**

**THROMBOSIS**
**T**rauma, travel
**H**ypercoagulable, HRT
**R**ecreational drugs (IVDU)
**O**ld (age >60 yr)
**M**alignancy
**B**irth control pill
**O**besity, obstetrics
**S**urgery, smoking
**I**mmobilization
**S**ickness (CHF, MI, nephrotic syndrome, vasculitis)

**Wells' Criteria for DVT**

| | |
|---|---|
| Active cancer | +1 |
| Paralysis, paresis or recent immobilization of leg | +1 |
| Recently bedridden x 3 d or major surgery within 4 wk | +1 |
| Local tenderness | +1 |
| Entire leg swollen | +1 |
| Calf swelling 3cm > asymptomatic leg | +1 |
| Unilateral pitting edema | +1 |
| Collateral superficial veins | +1 |
| Alternative Dx more likely | -2 |

0: Low probability
1-2: Moderate probability
>3: High probability

**Wells' Criteria for PE**

| | |
|---|---|
| Previous Hx of DVT/PE | +1.5 |
| HR >100 | +1.5 |
| Recent immobility or surgery | +1.5 |
| Clinical signs of DVT | +3 |
| Alternate Dx less likely than PE | +3 |
| Hemoptysis | +1 |
| Cancer | +1 |

<2: Low probability
2-6: Intermediate probability
>6: High probability

**PERC Score**

- Age >50 yr
- HR >100 bpm
- $O_2$ sat on RA <95%
- Prior history DVT/PE
- Recent trauma or surgery
- Hemoptysis
- Exogenous estrogen
- Clinical signs suggesting DVT

Score 1 for each question; a score 0/8 means patient has <1.6% chance having a PE and avoids further investigation. Caution using the PERC score in pregnant women as the original study excluded pregnant women

D-dimer is only useful if it is negative; negative predictive value >99%

- admit if hemodynamically unstable, require supplemental $O_2$, major comorbidities, lack of sufficient social supports, unable to ambulate, need invasive therapy
  - referral to medicine for coagulopathy and malignancy workup

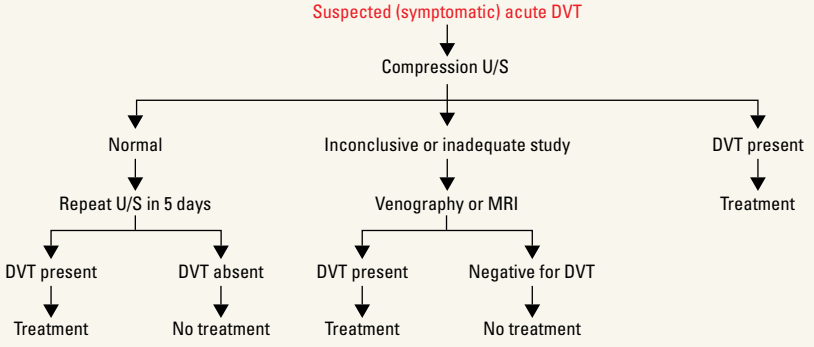



**Figure 12. Approach to suspected DVT**

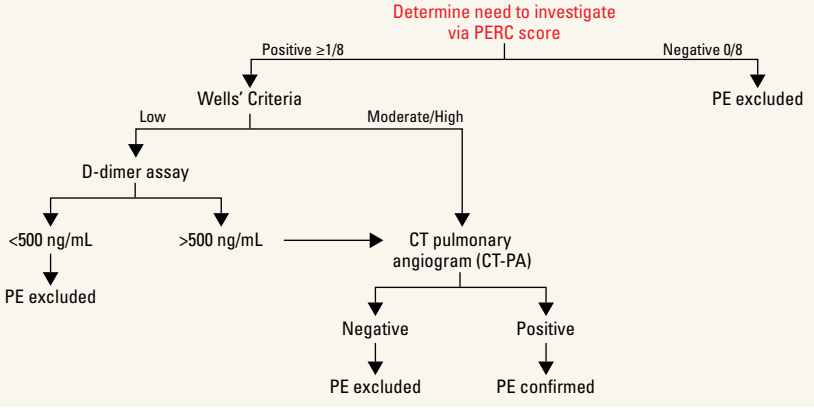



**Figure 13. Approach to suspected PE**

50% of patients with symptomatic proximal DVT will develop PE, often within days to weeks of the event

**Oral Direct Thrombin Inhibitors Or Oral Factor Xa Inhibitors For The Treatment Of Pulmonary Embolism**
Cochrane DB Syst Rev 2015:CD010957
**Objectives**: Assess effectiveness of oral direct thrombin inhibitors and oral factor Xa inhibitors for long-term treatment of PE.
**Methods**: Systematic review of RCTs in patients with confirmed PE receiving oral direct thrombin inhibitors or factor Xa inhibitors for minimum 3 mo.
**Results**: 5 RCTs, 7897 participants. No difference in the effectiveness of oral direct thrombin inhibitors vs. standard anticoagulation in preventing recurrent PE (OR 1.02, 95% CI 0.50-2.04), recurrent VTE (OR 0.93, 95% CI 0.52-1.66), DVT (OR 0.72, 95% CI 0.39-1.32), all-cause mortality (OR 1.16, 95% CI 0.79-1.70), or major bleeding (OR 0.97, 95% CI 0.59-1.62).
**Conclusions**: High quality evidence suggests there is no difference between oral direct thrombin inhibitors and standard anticoagulation in the prevention of recurrent pulmonary embolism. Moderate-high evidence suggests there is no difference in recurrent VTE, DVT, all-cause mortality, and major bleeding between DOACs and standard anticoagulation.

# Diabetic Emergencies

- see Endocrinology, E12

## Diabetic Ketoacidosis

- triad of hyperglycemia, ketosis, and acidosis due to severe insulin deficiency and counter-regulatory hormone excess
- clinical feature
  - often young, Type 1 DM patients (may rarely be first presentation of undiagnosed Type 2 DM), with symptoms evolving within a day
  - early signs and symptoms: polyuria, polydipsia, malaise, nocturia, weight loss
  - late signs and symptoms
    - GI: anorexia, nausea, vomiting, abdominal pain
    - neurological: fatigue, drowsiness, stupor, coma
    - respiratory: Kussmaul's respiration, dyspnea (often due to acidosis), fruity ketotic breath
- investigations
  - blood work: CBC, electrolytes, $Ca^{2+}$, $Mg^{2+}$, $PO_4^{3-}$, Cr, BUN, glucose, ketones, osmolality, AST/ALT/ALP, amylase, troponin
  - urine: glucose and ketones
  - ABG or VBG
  - ECG (MI is possible precipitant; electrolyte disturbances may predispose to dysrhythmia)
- management
  - rehydration
    - bolus of NS, then high rate NS infusion (beware of overhydration and cerebral edema, especially in pediatric patients)
    - beware of a pseudohyponatremia due to hyperglycemia (add 3 $Na^+$ per 10 glucose over 5.5 mmol/L)

- potassium
  - essential to avoid hypokalemia: replace KCl (20 mEq/L if adequate renal function and initial $K^+$ <5.5 mmol/L)
  - use cardiac monitoring if potassium levels normal or low
- insulin
  - critical, as this is the only way to inhibit gluconeogenesis/ketosis
  - do not give insulin if $K^+$ <3.3 mmol/L
  - followed by continuous infusion at 5-10 U (or 0.1 U/kg) per h
  - once the blood glucose <14 mmol/L, patient should receive their regular insulin SC injection and the infusion should be stopped in 1 h
  - add D5W to IV fluids when blood glucose <15 mmol/L to prevent hypoglycemia
- bicarbonate is not given unless patient is at risk of death or shock (typically pH <7.0)

**4 Criteria for DKA Dx**
- Hyperglycemia
- Metabolic acidosis
- Hyperketonemia
- Ketonuria

**Signs and Symptoms of DKA**
D: Diuresis, dehydration, drowsy, delirium, dizziness
K: Kusmaul's breathing, ketotic breath
A: Abdominal pain, anorexia

## Hyperosmolar Hyperglycemic State

- state of extreme hyperglycemia (44-133.2 mmol/L) due to relative insulin deficiency, counter-regulatory hormones excess, gluconeogenesis, and dehydration (due to osmotic diuresis)
- clinical feature
  - often older, Type 2 DM patients with more co-morbid illnesses and larger fluid losses with symptoms evolving over days to weeks, fewer GI symptoms and more neurological deficits than DKA including: mental disturbances, coma, delirium, seizures
  - polyuria, N/V
- investigations
  - blood work: CBC, electrolytes, $Ca^{2+}$, $Mg^{2+}$, $PO_4^{3-}$, Cr, BUN, glucose, ketones, osmolality
  - urine: glucose and ketones
  - ABG or VBG
  - find underlying cause: ECG, CXR, blood and urine C&S
- management
  - rehydration with IV NS (total water deficit estimated at average 100 cc/kg body weight)
  - $O_2$, cardiac monitoring, frequent electrolyte, and glucose monitoring
  - insulin is controversial
  - identify and treat precipitating factors, if present (the 5 Is)

**Precipitating Factors in DKA**

**The 5 Is**
**I**nfection
**I**schemia
**I**nfarction
**I**ntoxication
**I**nsulin missed

## Hypoglycemia

- characterized by Whipple's triad: low plasma glucose, symptoms suggestive of hypoglycemia, prompt resolution of symptoms when glucose administered
- clinical feature
  - neuroglycopenic symptoms: headaches, confusion, seizures, coma
  - autonomic symptoms: diaphoresis, nausea, hunger, tachycardia, palpitations
- history and physical exam
  - last meal, known DM, prior similar episodes, drug therapy, and compliance
  - liver/renal/endocrine/neoplastic disease
  - depression, alcohol or drug use
- management
  - IV access and rapid blood glucose measurement
  - D50W 50 mL IV push, glucose PO if mental status permits
  - if IV access not possible, glucagon 1-2 mg IM, repeat x 1 in 10-20 min
  - $O_2$, cardiac, frequent blood glucose monitoring
  - thiamine 100 mg IM (if alcohol abuse is suspected)
  - full meal as soon as mental status permits
  - if episode due to long-acting insulin, or sulfonylureas, watch for prolonged hypoglycemia due to long t1/2 (may require admission for monitoring)
  - search for cause (common causes include exogenous insulin, alcohol, or sulfonylureas)

**Causes of Hypoglycemia**
Most common: excessive insulin use in setting of poor PO intake
Common: alcohol intoxication, sepsis, liver disease, oral anti-hyperglycemics
Rare: insulinomas, hypopituitarism, adrenal insufficiency, med side effects

Cerebral edema may occur if hyperosmolality is treated too aggressively

# Electrolyte Disturbances

- see Nephrology, NP7

**Table 20. Electrolyte Disturbances**

| Electrolyte Disturbance | Common Causes | Symptoms | Treatment | Special Considerations |
|---|---|---|---|---|
| **Hypernatremia** | Inadequate $H_2O$ intake (elderly/disabled) or inappropriate excretion of $H_2O$ (diuretics, Li, and diabetes insipidus) | Lethargy, weakness, irritability, and edema; seizures and coma occur with severe elevations of $Na^+$ levels (>158 mmol/L) | Salt restrict and give normal saline until hemodynamically stable. Use half-normal saline once vitals are stable | No more than 12 mmol/L in 24 h drop in $Na^+$ (0.5 mmol/L/h) due to risk of cerebral edema, seizures, death |
| **Hyponatremia** | Hypovolemic (GI, renal, skin, blood fluid loss), euvolemic (SIADH/stress, adrenal insufficiency, hypothyroid, diet/intake), hypervolemic (CHF, cirrhosis, nephrotic syndrome) | Neurologic symptoms 2° to cerebral edema, headache, decreased LOC, depressed reflexes; chronic milder than acute | Hypovolemic: normal saline<br>Euvolemic: restrict water, eliminate underlying cause<br>Hypervolemic: restrict fluid and sodium, loop diuretic if severe.<br><br>3% hypertonic saline if seizure or coma | Limit total rise to 8 mmol/L in 24 h (0.25 mmol/L/h maximum) as patients are at risk of osmotic demyelinating syndrome (ODS) |
| **Hyperkalemia** | Rhabdomyolysis, insulin deficiency, metabolic acidosis (e.g. acute renal failure, missed dialysis) | Nausea, palpitations, muscle stiffness, areflexia | Protect heart: calcium gluconate<br>Shift $K^+$ into cells: D50W + Insulin, $NaHCO_3$, salbutamol<br>Remove $K^+$: Fluids+furosemide, dialysis | High risk of dysrhythmia - ECG: peaked/narrow T wave, decreased P wave, prolonged PR interval, widening of QRS, AV block, VFib |
| **Hypokalemia** | Metabolic alkalosis (e.g. diarrhea), insulin, diuretics, anorexia, salbutamol | N/V, fatigue, muscle cramps, constipation | K-Dur®, $K^+$ sparing diuretics, IV solutions with 20-40 mEq/L KCl over 3-4 h | ECG: U waves most important, flattened/inverted T waves, prolonged QT, depressed ST<br>May need to restore $Mg^{2+}$ |
| **Hypercalcemia** | Hyper-PTH and malignancy account for ~80% of cases | Multisystem including CVS, GI (groans), renal (stones), rheumatological, MSK (bones), psychiatric (moans) | Isotonic saline (+ furosemide if hypervolemic)<br>Bisphosphonates, dialysis, chelation (EDTA or oral $PO_4^{3-}$) | Patients with more severe or symptomatic hypercalcemia are usually dehydrated and require saline hydration as initial therapy |
| **Hypocalcemia** | Iatrogenic, hypoalbuminemia, liver dysfunction,1° hypo-parathyroid hormone | Laryngospasm, hyperreflexia, paresthesia, tetany, Chvostek's and Trousseau's sign | Acute (ionized $Ca^{2+}$ <0.7 mM) requires immediate treatment: IV calcium gluconate 1-2 g in 10-20 min followed by slow infusion | Prolonged QT interval can arise (leading to dysrhythmia as can upper airway obstruction) |

# Hypertensive Emergencies

## Hypertensive Emergency (Hypertensive Crisis)

- definition: severe elevation of BP with evidence of end-organ damage (CNS, retinal, CVS, renal, GI)
- etiology
  - essential HTN, emotional exertion, pain, use of sympathomimetic drugs (cocaine, amphetamine, etc.), MAOI use with ingestion of tyramine-containing food (cheese, red wine, etc.), pheochromocytoma, pregnancy
- clinical feature

**Table 21. Signs and Symptoms of Hypertensive Emergencies**

| | CNS | Retinal | Renal | Cardiovascular | Gastrointestinal |
|---|---|---|---|---|---|
| **Complication** | Stroke/TIA, headache, altered mental status, seizures, hemorrhage | Vision change, hemorrhage, exudates, papilledema | Nocturia, elevated Cr, proteinuria, hematuria, oliguria | Ischemia/angina, infarction, dissection (back pain), CHF | N/V, abdominal pain, elevated liver enzymes |

**HELLP Syndrome** (seen only in preeclampsia/eclampsia)
**H**emolytic anemia
**E**levated **L**iver enzymes
**L**ow **P**latelet count

**Catecholamine-Induced Hypertensive Emergencies**
Avoid use of non-selective β-blockers as they inhibit β-mediated vasodilation and leave α-adrenergic vasoconstriction unopposed

- investigations
  - blood work: CBC, electrolytes, BUN, Cr
  - urinalysis
  - peripheral blood smear: to detect microangiopathic hemolytic anemia
  - CXR: if SOB or chest pain
  - ECG, troponins, CK: if chest pain
  - CT head: if neurological findings or severe headache
  - toxicology screen if sympathomimetic overdose suspected
- management
  - in general, strategy is to gradually and progressively reduce BP in 24-48 h
  - lower BP by 25% over the initial 60 min by initiating antihypertensive therapy (usually nitroprusside and labetatol)
  - if preeclampsia, immediately consult OB/GYN (see Obstetrics, OB24)
  - establish arterial line; transfer to ICU for further reduction in BP under monitored setting
  - in case of ischemic stroke: do no rapidly reduce BP, maintain BP >150/100 for 5 d
  - in case of aortic dissection: rapid reduction of sBP to 110-120 STAT (do not resuscitate with IV fluids)
  - in case of excessive catecholamines: avoid β-blockers (except labetalol)
  - in case of ACS: address ischemia initially, then BP

### Hypertensive Urgency

- definition: severely elevated BP (usually sBP >180, dBP >110) with no evidence of end-organ damage
- most often caused by non-adherence to prescriptions
- treatment: re-initiate antihypertensive therapy, acute BP reduction not indicated
- goal: differentiate hypertensive emergencies from hypertensive urgencies



With CNS manifestations of severe HTN, it is often difficult to differentiate causal relationships (i.e. HTN could be secondary to a cerebral event with an associated Cushing reflex)

**Table 22. Commonly Used Agents for the Treatment of Hypertensive Crisis**

| Drug | Dosage | Onset of Action | Duration of Action | Adverse Effects* | Special Indications |
|---|---|---|---|---|---|
| **VASODILATORS** | | | | | |
| **Sodium Nitroprusside** (vascular smooth muscle dilator) 1st line | 0.25-10 µg/kg/min | Immediate | 3-5 min | N/V, muscle twitching, sweating, cyanide intoxication, coronary steal syndrome | Most hypertensive emergencies (especially CHF, aortic dissection)<br>Use in combination with β-blockers (e.g. esmolol) in aortic dissection<br>Caution with high ICP and azotemia |
| **Nicardipine** (CCB) | 2 mg IV bolus, then 4 mg/kg/h IV | 15-30 min | 40 min | Tachycardia, headache, flushing, local phlebitis (e.g. encephalopathy, renal failure, eclampsia, sympathetic crisis) | Most hypertensive emergencies<br>Caution with acute CHF |
| **Fenoldopam Mesylate** (dopamine receptor antagonist) | 0.05-0.1 µm/kg/min IV | <5 min | 8-10 min | Tachycardia, headache, nausea, flushing (e.g. acute RF) | Most hypertensive emergencies<br>Caution with glaucoma |
| **Enalapril** (ACEI) | 0.625-1.25 mg IV q6h | 15-30 min | 12-24 h | Theoretical fall in pressure in high renin states not seen in studies | Acute LV failure<br>Avoid in acute MI, pregnancy, acute RF |
| **Nitroglycerin** | 5-20 µg/min IV | 1-2 min | 3-5 min | Hypotension, bradycardia, headache, lightheadedness, dizziness | MI/pulmonary edema |
| **Hydralazine** | 5-10 mg IV/IM q20min (max 20 mg) | 5-20 min | 2-6 h | Dizziness, drowsiness, headache, tachycardia, $Na^+$ retention | Eclampsia |
| **ADRENERGIC INHIBITORS** | | | | | |
| **Labetalol** | 20 mg IV bolus q10min or 0.5-2 mg/min | 5-10 min | 3-6 h | Vomiting, scalp tingling, burning in throat, dizziness, nausea, heart block, orthostatic hypotension | Most hypertensive emergencies (especially eclampsia)<br>Avoid in acute CHF, heart block >1st degree |
| **Esmolol** | 250-500 µg/kg/min 1 min, then 50 µg/kg/min for 4 min; repeat | 1-2 min | 10-20 min | Hypotension, nausea, bronchospasm | Aortic dissection, acute MI SVT dysrhythmias, perioperative HTN<br>Avoid in acute CHF, heart block >1st degree |
| **Phentolamine** | 5-15 mg q5-15min | 1-2 min | 3-10 min | Tachycardia, headache, flushing | Catecholamine excess (e.g. pheochromocytoma) |

*Hypotension may occur when using any of these agents

## Acute Coronary Syndrome

- see Cardiology and Cardiac Surgery, C27
- definition: new onset of chest pain, or acute worsening of previous chest pain, or chest pain at rest with:
  - negative cardiac biomarkers and no ECG changes = Unstable angina (UA)
  - positive cardiac biomarkers (elevated troponin) and NSTEMI (or ECG changes without ST elevation)
  - positive cardiac biomarkers (elevated troponin) and ST segment elevation on ECG = STEMI
- investigations
  - ECG STAT (as soon as history suggests possible ACS), troponin (2-6 h after symptom onset), CXR (to rule out other causes of the patient's presentation)
- management
  - stabilize: ABCs, oxygen, IV access, cardiac monitors, oximetry
  - ASA 162-325 mg chewed and swallowed
  - nitroglycerin 0.3 mg SL q5min x 3; IV only if persistent pain, CHF, or hypertensive
    - contraindications: hypotension, phosphodiesterase inhibitor use, right ventricular infarctions (1/3 of all inferior MIs)

- anticoagulation: choice of anticoagulation (unfractionated heparin, LMWH, or fondaparinux) and additional antiplatelet therapy (clopidogrel, ticagrelor, or prasugrel) depends on STEMI vs. NSTEMI and reperfusion strategy
- early cardiology consult for reperfusion therapy
  - UA/NSTEMI: early coronary angiography recommended if high TIMI risk score
  - STEMI: primary percutaneous coronary intervention (within 90 min) preferred; thrombolytics if PCI unavailable within 120 min of medical contact, symptoms <12 h and no contraindications
- atorvastatin 80 mg to stabilize plaques
- β-blocker if no signs of CHF, hemodynamic compromise, bradycardia, or severe reactive airway disease
- ACEI initiated within 24 h

# Sepsis

- see Infectious Diseases, ID19 and Respirology, R30
- definitions
  - sepsis: life-threatening organ dysfunction caused by a dysregulated host response to infection
- organ dysfunction defined as a change in baseline SOFA score ≥2 points
  - septic shock: profound circulatory, cellular, and metabolic abnormalities with greater risk of mortality than with sepsis alone
- require vasopressors to maintain MAP ≥65 mmHg
- associated with serum lactate ≥2 mmol/L without hypovolemia
- management
  - early recognition of sepsis and investigations to locate source of infection
  - identify severe sepsis with lactate or evidence of tissue hypoperfusion
  - early "goal-directed" therapy: ensure adequate organ perfusion
  - treatment priorities:
    - ABCs, monitors, lines
    - aggressive fluid resuscitation; consider ventilatory and inotropic support
    - cultures, then early empiric appropriate antibiotics - consider broad spectrum and atypical coverage
    - source control - e.g. remove infected Foley or surgery for ischemic gut
    - monitor adequate resuscitation with vital signs, inferior vena cava on U/S, and serial measurement of serum lactate

# Stroke and Transient Ischemic Attack

- see Neurology, N48
- definitions
  - stroke: sudden loss of brain function due to ischemia (87%) or hemorrhage (13%) with persistence of symptoms >24 h or neuroimaging evidence
  - TIA: transient episode of neurologic dysfunction from focal ischemia without acute infarction or neuroimaging evidence
- clinical feature

**Table 23. Signs and Symptoms of Stroke**

| | General | Language/ Throat | Vision | Coordination | Motor | Sensation | Reflex |
|---|---|---|---|---|---|---|---|
| **Signs/ Symptoms** | Decreased LOC, changed mental status, confusion, neglect | Dysarthria, aphasia, swallowing difficulty | Diplopia, eye deviation, asymmetric pupils, visual field defect | Ataxia, intention tremor, lack of coordination | Increased tone, loss of power, spasticity | Loss of sensation | Hyper-reflexia, clonus |

- patients with hemorrhagic stroke can present with sudden onset thunderclap headache that is usually described as "worst headache of life"
- stroke mimickers: seizure, migraine, hypoglycemia, Todd's paresis, peripheral nerve injury, Bell's palsy, tumour, syncope

**Table 24. Stroke Syndromes**

| Region of Stroke | Stroke Syndrome |
|---|---|
| **ACA** | Contralateral hemianesthesia and hemiparesis (legs > arms/face), gait apraxia, altered mental status, impaired judgement |
| **MCA** | Contralateral hemianesthesia and hemiparesis (arms/face > legs), contralateral homonymous hemianopsia, ipsilateral gaze |
| **PCA** | Contralateral homonymous hemianopsia, cortical blindness, impaired memory |
| **VBA** | Wide variety of cranial nerve, cerebellar, and brainstem deficits: vertigo, nystagmus, diplopia, visual field deficits, dysphagia, dysarthria, facial hypoesthesia, syncope, ataxia<br>Loss of pain and temperature sensation in ipsilateral face and contralateral body |



**7 Causes of Emboli from the Heart**
- AFib
- MI
- Endocarditis
- Valvular disease
- Dilated cardiomyopathy
- Left heart myxoma
- Prosthetic valves



**Differentiation of UMN Disease vs. LMN Disease**

| Category | UMN Disease | LMN Disease |
|---|---|---|
| Muscular deficit | Muscle groups | Individual muscles |
| Reflexes | Increased | Decreased/ absent |
| Tone | Increased | Decreased |
| Fasciculations | Absent | Present |
| Atrophy | Absent/ minimal | Present |
| Plantar Response | Upgoing | Downgoing |

### Investigations
- CBC, electrolytes, blood glucose, coagulation studies ± cardiac biomarkers ± toxicology screen
- non-contrast CT head: look for hemorrhage, ischemia
- ECG ± echocardiogram: rule out AFib, acute MI as source of emboli
- other imaging: carotid Doppler, CTA, MRA as appropriate

### Management
- ABCs; intubation with RSI if GCS ≤8, rapidly decreasing GCS, or inadequate airway protection reflexes
- thrombolysis: immediate assessment for eligibility; need acute onset, <4.5 h from drug administration time AND compatible physical findings AND normal CT with no bleed
- elevating head of bed if risk of elevated ICP, aspiration, or worsening cardiopulmonary status
- NPO, IV ± cardiac monitoring
  - judge fluid rate carefully to avoid overhydration (cerebral edema) as well as underhydration (underperfusion of the ischemic penumbra)
- BP control: only treat severe HTN (sBP >200 mmHg, dBP >120 mmHg, mean arterial BP >140 mmHg) or HTN associated with hemorrhagic stroke transformation, cardiac ischemia, aortic dissection, or renal damage; use IV nitroprusside or labetalol
- glycemic control: keep fasting glucose <6.5% in acute phase (5 d)
- cerebral edema control: hyperventilation, mannitol to decrease ICP if necessary
- consult neurosurgery, neurology, medicine as indicated

### Medications
- acute ischemic stroke: thrombolytics (rt-PA, e.g. alteplase) if within 4.5 h of symptom onset with no evidence of hemorrhage on CT scan
- antiplatelet agents: prevent recurrent stroke or stroke after TIAs, e.g. Aspirin® (1st line); clopidogrel, Aggrenox® (2nd line)
- anticoagulation: DVT prophylaxis if immobile; treat AFib if present
- follow-up for consideration of carotid endarterectomy, cardiovascular risk optimization

If patient presents within 4.5 h of onset of disabling neurological deficits greater than 60 min with no signs of resolution, they may be a candidate for thrombolysis. Do brief assessment and order stat CT head

**Absolute Exclusion Criteria for tPA**
- Suspected subarachnoid hemorrhage
- Previous intracranial hemorrhage
- Cerebral infarct or severe HI within the past 3 mo
- BP >185 mmHg systolic, or >110 mmHg diastolic
- Bleeding diathesis
- Prolonged PT >15 s or INR >1.7
- Platelet count <100,000
- Heparin received within last 48 h
- Current use of thrombin inhibitors or direct factor Xa inhibitors
- Blood glucose <2.8 mmol/L (<50 mg/dL)
- Intracranial hemorrhage on CT or large volume infarct

**Relative Exclusion Criteria for tPA**
- Only minor or rapidly improving symptoms
- Pregnancy
- GI or urinary hemorrhage within the past 21 d
- Seizure at onset causing postictal impairments

# Otolaryngological Presentations and Emergencies

- see Otolaryngology, OT6
- ear symptoms: otalgia, aural fullness, otorrhea, hearing loss, tinnitus, vertigo, pruritis, fever
- risk factors for hearing loss: Q-tip use, hearing aids, headphones, occupational noise exposure

### Dizziness and Vertigo
- distinguish four types of dizziness: vertigo ("room spinning"), lightheadedness ("disconnected from environment"), presyncope ("almost blacking out"), dysequilibrium ("unstable, off-balance")
- broad differential and diverse management (see Family Medicine, FM25 and Otolaryngology, OT12)
- consider adverse drug events

### Otalgia (see Otolaryngology, OT6)
- differential diagnosis
  - infections: acute otitis externa, acute otitis media, otitis media with effusion, mastoiditis, myringitis, malignant otitis externa in diabetics, herpes simplex/zoster, auricular cellulitis, external canal abscess, dental disease
  - others: trauma, temporomandibular joint dysfunction, neoplasm, foreign body, cerumen impactions, trigeminal neuralgia, granulomatosis with polyangiitis
- inspect for otorrhea, palpate outer ear/mastoid, otoscopic examination to look for bulging erythematous tympanic membrane, perforation, membrane retraction, infiltration, vesicles, ulcers, masses, lesions
- C&S of ear canal discharge, if present
- CT head if suspicion of mastoiditis, malignant otitis externa
- antibiotics/antifungals/antivirals for respective infections

### Hearing Loss (see Otolaryngology, OT7)
- differentiate conductive vs. sensorineural hearing loss
- rule out sudden sensorineural hearing loss (SSNHL), a medical emergency requiring high dose steroids and urgent referral
- an elderly patient presenting with unilateral tinnitus or SNHL must be presumed to have an acoustic neuroma (vestibular schwannoma) until proven otherwise
- consider audiogram and referral to or follow-up with family physician

# Epistaxis

- see Otolaryngology, OT26
- 90% of nosebleeds stem from the anterior nasal septum (Kiesselbach's plexus located in Little's area)
- can be life-threatening

### Etiology
- most cases of epistaxis are caused by trauma (digital, blunt, foreign bodies)
- other causes: barometric changes, nasal dryness, chemicals (cocaine, Otrivin®), or systemic disease (coagulopathies, HTN, etc.)

### Investigations
- blood work: CBC, PT/PTT (as indicated)
- imaging: X-ray, CT as needed

### Treatment
- goals of treatment: localize bleeding and achieve hemostasis
- first-aid: ABCs, clear clots by blowing nose or suctioning, lean forward, pinch cartilaginous portion of nose for 20 min twice
- assess blood loss: vitals, IV NS, cross match 2 units pRBC if significant
- if first aid measures fail twice, proceed to packing
- apply an anterior pack
  - clear nose of any clots
  - apply topical anesthesia/vasoconstrictors (lidocaine with epinephrine, cocaine, or soaked pledgets)
  - insert either a traditional Vaseline® gauze pack or a commercial nasal tampon or balloon
  - if bleeding stops, arrange follow-up in 48-72 h for reassessment and pack removal
  - if packing both nares, prophylactic anti-staphylococcal antibiotics to prevent sinusitis or toxic shock syndrome
  - if bleeding is not controlled with anterior pressure, cautery with silver nitrate can be performed if the site of bleeding is identified (only cauterize one side of the septum because if both are cauterized this can lead to septal perforation)
- if suspect posterior bleed or anterior packing does not provide hemostasis, consult ENT for posterior packing and further evaluation
  - posterior packing requires monitoring; can cause significant vagal response and posterior bleeding source can lead to significant blood loss, therefore usually requires admission

### Disposition
- discharge: discharged upon stabilization and appropriate follow-up; educate patients about prevention (e.g. humidifiers, saline spray, avoiding irritants, managing HTN)
- admission: severe cases of refractory bleeding, and most cases of posterior packing

Thrombocytopenic patients – use resorbable packs to avoid risk of re-bleeding caused by pulling out the removable pack

**Complications of Nasal Packing**
- Hypoxemia
- Toxic-shock syndrome
- Aspiration
- Pharyngeal fibrosis/stenosis
- Alar/septal necrosis

**Tranexamic Acid For Patients With Nasal Haemorrhage (Epistaxis)**
Cochrance DB Syst Rev 2018:CD004328
**Objectives**: Determine the effects of tranexamic acid compared to placebo, no additional intervention or any other haemostatic agent in the management of patients with epistaxis.
**Methods**: Systematic review of RCTs comparing tranexamic acid, in addition to standard care, compared to usual care plus placebo in adults and children.
**Results**: 6 RCTs, 692 participants. Oral (RR 0.73, 95% CI 0.55-0.96) and topical (RR 0.66, 95% CI 0.41-1.05) reduced risk of re-bleeding compared to placebo. There was no difference in time to stop initial bleeding. The proportion of patients whose bleeding stopped within 10 minutes was higher with topical tranexamic acid than other hemostatic agents (RR 2.35, 95% CI 1.90-2.92).
**Conclusions**: Moderate-quality evidence that risk of re-bleeding with oral or topical tranexamic acid, in addition to usual care, is lower in adult patients with epistaxis, compared to placebo with usual care. Further, topical tranexamic acid is probably better than other topical agents in stopping bleeding in the first 10 minutes.

# Gynecologic/Urologic Emergencies

## Vaginal Bleeding

- see Gynecology, GY9 and Obstetrics, OB13

### Etiology
- pregnant patient
  - 1st/2nd trimester: ectopic pregnancy, abortion (threatened, incomplete, complete, missed, inevitable, septic), molar pregnancy, implantation bleeding, friable cervix (most common cause)
  - 2nd/3rd trimester: placenta previa, placental abruption, premature rupture of membranes, preterm labour
  - other: trauma, bleeding cervical polyp, passing of mucous plug
- postpartum
  - postpartum hemorrhage, uterine inversion, retained placental tissue, endometritis
- non-pregnant patients
  - structural (PALM- polyps, adenomyosis, leiomyoma, malignancies/hyperplasia)
  - non-structural (COEIN - coagulopathy, ovulatory, endometrial, iatrogenic, NYD)

### History
- characterize bleeding (frequency, duration, number of pads/tampons, types of pads used, cyclicity)
- pain, if present (OPQRSTUV)
- menstrual history, sexual history, STI history, syncope/pre-syncope, malignancy history, family history, hematological history, cardiac history, abdo history
- details of pregnancy, including gush of fluid and fetal movement (>20 wk)

### Physical Exam
- ABC (especially noting postural BP/HR and mucous membranes)
- abdominal examination (signs of peritoneal pathology, tenderness, distension, mass)
- speculum examination (NOT IF 2nd/3rd trimester bleeding; perform only if placenta previa has been ruled out with U/S)
  - look for active bleeding, trauma/anomaly, and cervical dilatation
- bimanual examination (cervical motion tenderness, size of uterus, cervical length/dilatation)
- sterile gloves and speculum if pregnant
- POCUS: rule in intra-uterine or ectopic pregnancy, check for free fluid in pelvis/RUQ/LUQ, consider assessment of fluid responsiveness (intra-hepatic IVC collapsibility, carotid flow measurement)

### Investigations
- β-hCG test for all patients with childbearing potential
- CBC, blood and Rh type, quantitative β-hCG, PTT, INR
- type & cross if significant blood loss
- transvaginal U/S (rule out ectopic pregnancy and spontaneous abortion)
- abdominal U/S (rule out placenta previa, fetal demise, or retained products post-partum)

### Management
- ABCs
- pulse oximeter and cardiac monitors if unstable
- Rh immune globulin (Rhogam®) for vaginal bleeding in pregnancy and Rh-negative mother
- 1st/2nd trimester pregnancy
  - ectopic pregnancy: definitive treatment with surgery or methotrexate
  - intrauterine pregnancy, no concerns of coexistent ectopic: discharge patient with obstetrics follow-up
  - U/S indeterminate or β-hCG >1000-2000 IU: further workup and/or gynecology consult
  - abortions: if complete, discharge if stable; for all others, consult gynecology
- 2nd/3rd trimester pregnancy
  - placenta previa or placental abruption: obstetrics consult for possible admission
- postpartum
  - manage ABCs: start 2 large bore IV rapid infusion, type & cross 4 units of blood, consult OB/GYN immediately
- non-pregnant
  - if unstable admit to gynecology for IV hormonal therapy, possible D&C
  - non-structural abnormalities
    - tranexamic acid to stabilize clots
    - medroxyprogesterone acetate 10 mg PO OD x 10d, warn patient of a withdrawal bleed
  - stable structural abnormalities (fibroids, polyps, endometrial thickening, adenomyosis), outpatient gynecology referral once stable

### Disposition
- decision to admit or discharge should be based on the stability of the patient, as well as the nature of the underlying cause; consult OB/GYN for patients requiring admission
- if patient can be safely discharged, ensure follow-up with family physician or gynecologist
- instruct patient to return to ED for increased bleeding, presyncope

Vaginal bleeding can be life-threatening Always start with ABCs and ensure your patient is stable

Need β-hCG ≥1200 to see intrauterine changes on transvaginal U/S

An ectopic pregnancy can be ruled out by confirming an intrauterine pregnancy by bedside U/S unless the patient is using IVF due to the high risk of heterotopic pregnancy

Vaginal bleeding (and its underlying causes) can be a very distressing event for patients; ensure appropriate support is provided

## Pregnant Patient in the ED

**Table 25. Complications of Pregnancy**

| Trimester | Fetal | Maternal |
|---|---|---|
| **First**<br>**1-12 wk** | Pregnancy failure<br>Spontaneous abortion<br>Fetal demise<br>Gestational trophoblastic disease | Ectopic pregnancy<br>Anemia<br>Hyperemesis gravidarum<br>UTI/pyelonephritis |
| **Second**<br>**13-27 wk** | Disorders of fetal growth<br>IUGR<br>Oligo/polyhydramnios | Gestational DM<br>Rh incompatibility<br>UTI/pyelonephritis |
| **Third**<br>**28-41 wk** | Vasa previa | Preterm labour/PPROM<br>Preeclampsia (hypertension in pregnancy)/eclampsia<br>Placenta previa<br>Placental abruption<br>Uterine rupture<br>DVT/PE |

# Nephrolithiasis (Renal Colic)

• see Urology, U18

### Epidemiology and Risk Factors
- 10% of population (twice as common in males)
- recurrence 50% at 5 yr
- peak incidence 30-50 yr of age
- 75% of stones <5 mm pass spontaneously within 2 wk, larger stones may require consultation

**Kidney Stones**
- 80% Calcium oxalate
- 10% Struvite
- 10% Uric acid

### Clinical Features
- urinary obstruction → upstream distention of ureter or collecting system → severe colicky pain
- may complain of pain at flank, groin, testes, or tip of penis
- writhing, N/V, hematuria (90% microscopic), diaphoresis, tachycardia, tachypnea
- occasionally symptoms of trigonal irritation (frequency, urgency)
- fever, chills, rigors in secondary pyelonephritis
- peritoneal findings/anterior abdominal tenderness usually absent

**Obstruction + Infection**
= Urological Emergency
Urgent urology consult

### Differential Diagnosis of Renal Colic
- acute ureteric obstruction
- acute abdomen: biliary, bowel, pancreas, AAA
- urogynecological: ectopic pregnancy, torsion/rupture of ovarian cyst, testicular torsion
- pyelonephritis (fever, chills, pyuria, vomiting)
- radiculitis (L1): herpes zoster, nerve root compression

### Investigations
- CBC: elevated WBC in presence of fever may support an infectious cause
- electrolytes, Cr, BUN to assess renal function
- U/A: R&M (WBCs, RBCs, crystals), C&S
- non-contrast spiral CT is the study of choice
- abdominal U/S may demonstrate stone(s), hydronephrosis (consider in females of childbearing age or if patient has another contraindication to CT scanning), debris in the collecting system, reduced cortical vascularity, abnormal renal parenchyma
- AXR will identify large radioopaque stones (calcium, struvite, and cystine stones) but may miss smaller stones, uric acid stones, or stones overlying bony structures; consider as an initial investigation in patients who have a history of radioopaque stones and similar episodes of acute flank pain (CT necessary if film is negative)
- strain all urine for stone analysis

**Indications for Admission to Hospital**
- Intractable pain
- Fever (suggests infection) or other evidence of pyelonephritis
- Single kidney with ureteral obstruction
- Bilateral obstructing stones
- Intractable vomiting
- Compromised renal function

### Management
- analgesics: NSAIDs (usually ketorolac [Toradol®], preferable over opioids), antiemetics, IV fluids if indicated
- urology consult may be indicated, especially if stone >5 mm, or if patient has signs of obstruction or infection
- α-blocker (e.g. tamsulosin) may be helpful to increase stone passage in select cases

### Disposition
- most patients can be discharged
- ensure patient is stable, has adequate analgesia, and able to tolerate oral medications
- may advise hydration and limitation of protein, sodium, oxalate, and alcohol intake

# Ophthalmologic Emergencies

• see Ophthalmology, OP5

### History and Physical Exam
- patient may complain of pain, tearing, itching, redness, photophobia, foreign body sensation, trauma
- mechanism of foreign body insertion – if high velocity injury suspected (welding, metal grinding, metal striking metal), must obtain orbital X-rays, U/S, or CT scan to exclude presence of intraocular metallic foreign body
- ask about sexual partners and exposure of eye(s) to bodily fluids (semen, urine, blood, vaginal fluids, saliva, etc.)
- visual acuity in both eyes, pupils, extraocular structures, fundoscopy, tonometry, slit lamp exam

Visual acuity is the "vital sign" of the eyes and should ALWAYS be assessed and documented in both eyes when a patient presents to the ER with an ophthalmologic complaint

### Management of Ophthalmologic Foreign Body
- copious irrigation with saline for any foreign body
- remove foreign body under slit lamp exam with cotton swab or sterile needle
- antibiotic drops qid until healed
- patching may not improve healing or comfort – do not patch contact lens wearers
- limit use of topical anesthetic to examination only (the evidence for this is mixed; if uncertain, ask ophthalmology)
- consider tetanus prophylaxis
- ophthalmology consult if globe penetration suspected

**Table 26. Differential Diagnosis of Red Eye in the Emergency Department**

| Symptom | Possible Serious Etiology |
|---|---|
| **Light Sensitivity** | Iritis, keratitis, abrasion, ulcer |
| **Unilateral** | Above + herpes simplex, acute angle closure glaucoma |
| **Significant Pain** | Above + scleritis |
| **White Spot on Cornea** | Corneal ulcer |
| **Non-Reactive Pupil** | Acute glaucoma, iritis |
| **Copious Discharge** | Gonococcal conjunctivitis |
| **Blurred Vision** | All of the above |

**Contraindications to Pupil Dilation**
- Shallow anterior chamber
- Iris-supported lens implant
- Potential neurological abnormality requiring pupillary evaluation
- Caution with CV disease – mydriatics can cause tachycardia

**Table 27. Select Ophthalmologic Emergencies**

| Condition | Signs and Symptoms | Management |
|---|---|---|
| **Acute Angle Closure Glaucoma** | Unilateral red, painful eye<br>Decreased visual acuity, halos around lights<br>Fixed, mid-dilated pupil<br>N/V<br>Marked increase in IOP (>40 mmHg)<br>Shallow anterior chamber ± cells | Ophthalmology consult for laser iridotomy<br>Medications: AABCDE/EAT PAL<br>Alpha agonist: epinephrine<br>Alpha2 agonist: apraclonide<br>Beta blocker: timolol<br>Cholinomimetic: pilocarpine<br>Diuretic: acetazolamide, mannitol<br>Eicosanoid: latanoprost |
| **Chemical Burn** | Known exposure to acids or alkali (worse)<br>Pain, decreased visual acuity<br>Vascularization or defects of cornea<br>Iris and lens damage | Irrigate site of accident with NS with eyelid retracted until neutral pH achieved.<br>Sweep fornices<br>Cycloplegic drops and topical antibiotics |
| **Orbital Cellulitis** | Red, painful eye, decreased visual acuity<br>Headache, fever<br>Lid erythema, edema, and difficulty opening eye<br>Conjunctival injection and chemosis<br>Proptosis, opthalmoplegia ± RAPD | Admission, ophthalmology consult<br>Blood cultures, orbital CT<br>IV antibiotics (ceftriaxone+ vancomycin)<br>Drainage of abscess |
| **Retinal Artery Occlusion** | Sudden, painless, monocular vision loss<br>RAPD<br>Cherry red spot and retinal pallor on fundoscopy if central retinal artery occlusion | Restore blood flow <2 h<br>Massage globe<br>Decrease IOP (topical β-blockers, inhaled $O_2$/$CO_2$ mix, IV Diamox®, IV mannitol, drain aqueous fluid) |
| **Retinal Detachment** | Flashes of light, floaters, and curtains of blackness/ peripheral vision loss<br>Painless<br>Loss of red reflex, decreased IOP<br>Detached areas are grey<br>Visible detachment orbital POCUS<br>± RAPD | Ophthalmology consult for scleral buckle/ pneumatic retinoplexy |

**Other Ophthalmologic Emergencies**
**Infectious**: Red eye, endophthalmitis, hypopyon
**Trauma**: Globe rupture, orbital blow-out fractures, corneal injuries, eyelid laceration, hyphema, lens dislocation, retrobulbar hemorrhage
**Painful vision loss**: Acute iritis, corneal abrasion, globe rupture, lens dislocation, retrobulbar hemorrhage, optic neuritis, temporal arteritis, endophthalmitis, keratitis
**Painless vision loss**: Central retinal vein occlusion, amaurosis fugax, occipital stroke

# Dermatologic Emergencies

## Rash Characteristics

### A. Diffuse Rashes

- Staphylococcal Scalded Skin Syndrome (SSSS)
  - caused by an exotoxin from infecting strain of coagulase-positive S. aureus
  - mostly occurs in children
  - prodrome: fever, irritability, malaise, and skin tenderness
  - sudden onset of diffuse erythema: skin is red, warm, and very tender
  - flaccid bullae that are difficult to see, then desquamate in large sheets
- Steven-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
  - see Dermatology, D22
  - caused by drugs (e.g. phenytoin, sulfas, penicillins, and NSAIDs), bone marrow transplantation, and blood product transfusions
  - usually occurs in adults
  - diffuse erythema followed by necrosis
  - severe mucous membrane blistering
  - entire epidermis desquamation
  - high mortality (>50%)
- Toxic Shock Syndrome (TSS)
  - see Infectious Diseases, ID21
  - caused by superantigen from S. aureus or GAS activating T-cells and cytokines
  - patient often presents with onset of shock and multi-organ failure, fever
  - diffuse erythematous macular rash
  - at least 3 organ systems involved: CNS, respiratory, GI, muscular, mucous membranes, renal, liver, hematologic, and skin (necrotizing fasciitis, gangrene)

- vesicobullous lesions
- Erythema Multiforme (EM)
  - immunologic reaction to herpes simplex
  - viral prodrome 1-14 d before rash
  - target lesion: central grey bulla or wheal surrounded by concentric rings of erythema and normal skin

**B. Discrete Lesions**

- pyoderma gangrenosum
  - often associated with IBD, rheumatoid conditions, leukemia, and monoclonal gammopathies.
  - often occurs in arms, hands, feet, or perineal region
  - usually begins as painless macule/vesicle/pustule/bulla on red/blue base sloughing, leaving a gangrenous ulcer
- disseminated gonococcal infection
  - see Dermatology, D32
  - fever, skin lesions (pustules/vesicles on erythematous base ~5 mm in diameter), arthritis (joint swelling and tenderness), and septic arthritis (in larger joints, such as knees, ankles, and elbows)
  - most commonly in gonococcus-positive women during menstruation or pregnancy
  - skin lesions usually appear in extremities and resolve quickly (<7 d)
- meningococcemia
  - flu-like symptoms of headache, myalgia, N/V
  - petechial, macular, or maculopapular lesions with grey vesicular centres
  - usually a few millimeters in size, but may become confluent and hemorrhagic
  - usually appear in extremities, but may appear anywhere
  - look for signs of meningeal irritation: positive jolt accentuation test, Brudzinski, Kernig

## History and Physical Exam

- determine onset, course, and location of skin lesions
- fever, joint pain
- associated symptoms: CNS, respiratory, GU, GI, renal, liver, mucous membranes
- medications, sexual encounters, living environment, occupational exposures
- vitals, physical exam based on relevant history

## Investigations

- immediate consultation if patient unstable
- case-dependent, consider: CBC, electrolytes, Cr, AST, ALT, ALP, blood culture, skin biopsy, serum immunoglobulin levels (serum IgE)



Thorough dermatologic examinations are required; examination of asymptomatic skin may identify more lesions; ensure adequate draping during dermatologic examinations

## Management

- general: judicious IV fluids and electrolyte control, consider vasopressors if hypotensive, prevention of infection
- determine if admission and consult needed: dermatology or infectious diseases
- specific management is determined by etiology
  - SSSS, TSS, DGI, and meningococcemia
    - IV antibiotics
  - EM, SJS, and TEN
    - stop precipitating medication
    - fluids
    - symptomatic treatment: antihistamines, antacids, topical corticosteroids, systemic corticosteroids (controversial), prophylactic oral acyclovir, consider IVIG, plasmapheresis
    - TEN: debride necrotic tissue



SJS = <10% of BSA
SJS/TEN = 10-30% BSA
TEN = >30% BSA

## Disposition

- most cases will require urgent care and hospitalization
- SJS & TEN: early transfer to burn centre improves outcome

# Environmental Injuries

## Heat Exhaustion and Heat Stroke

### HEAT EXHAUSTION

- clinical features relate to loss of circulating volume caused by exposure to heat stress
- "water depletion": heat exhaustion occurs if lost fluid not adequately replaced
- "salt depletion": heat exhaustion occurs when losses replaced with hypotonic fluid

Heat exhaustion may closely resemble heat stroke; heat exhaustion may eventually progress to heat stroke, so if diagnosis is uncertain treat as heat stroke

### HEAT STROKE

- life-threatening emergency resulting from failure of normal compensatory heat-shedding mechanisms
- divided into classical and exertional subtypes
- if patient does not respond relatively quickly to cooling treatments, consider other possible etiologies of hyperpyrexia (e.g. meningitis, thyroid storm, anticholinergic poisoning, delirium tremens, infections), adverse drug events (including drug interactions)

**Table 28. Heat Exhaustion vs. Heat Stroke**

| | Heat Exhaustion | Classical Heat Stroke | Exertional Heat Stroke |
|---|---|---|---|
| **Clinical Features** | Non-specific malaise, headache, fatigue<br>Body temp <40.5°C (usually normal)<br>No coma or seizures<br>Dehydration (HR, orthostatic hypotension) | Occurs in setting of high ambient temperatures (e.g. heat wave, poor ventilation)<br>Often patients are older, poor, and sedentary or immobile<br>Dry, hot skin<br>Temp usually >40.5°C<br>Altered mental status, seizures, delirium, or coma<br>May have elevated AST, ALT | Occurs with high endogenous heat production (e.g. exercise) that overwhelms homeostatic mechanisms<br>Patients often younger, more active<br>Skin often diaphoretic<br>Other features as for classical heat stroke, but may also have DIC, acute renal failure, rhabdomyolysis, marked lactic acidosis |
| **Treatment** | Rest in a cool environment<br>IV NS if orthostatic hypotension; otherwise replace losses slowly PO | Cool body temperature with water mist (e.g. spray bottle) and standing fans<br>Ice water immersion also effective; monitor body temperature closely to avoid hypothermic overshoot<br>Secure airway because of seizure and aspiration risk<br>Give fluid resuscitation if still hypotensive after above therapy<br>Avoid β-agonists (e.g. epinephrine), peripheral vasoconstriction, and antipyretics (e.g. ASA) | |

## Hypothermia and Cold Injuries

### HYPOTHERMIA

- hypothermia is defined as a core temperature below 35°C, in which the body's heat loss is greater than heat production
- predisposing risk factors: ethanol use, homelessness, psychiatric disease, and older age (the elderly have increased risk due to decreased physiological reserve, chronic diseases, medication side effects, and social isolation)
- treatment based on re-warming and supporting cardiorespiratory function
- complications: coagulopathy, acidosis, ventricular dysrhythmias (VFib), asystole, volume, and electrolyte depletion
- labs: CBC, electrolytes, ABG, serum glucose, Cr/BUN, $Mg^{2+}$, $Ca^{2+}$, amylase, coagulation profile
- imaging: CXR (aspiration pneumonia, pulmonary edema are common)
- monitors: ECG, rectal thermometer, Foley catheter, NG tube, monitor metabolic status frequently

**Afterdrop Phenomenon**
Warming of extremities causes vasodilation and movement of cool pooled blood from extremities to core, resulting in a drop in core temperature leading to cardiac arrest

**Table 29. Classification of Hypothermia**

| Class | Temp | Symptoms/Signs |
|---|---|---|
| **Mild** | 32-34.9°C | Tachypnea, tachycardia, ataxia, dysarthria, shivering |
| **Moderate** | 28-31.9°C | Loss of shivering, dysrhythmias, Osborne (J) waves on ECG, decreased LOC, combative behaviour, muscle rigidity, dilated pupils |
| **Severe** | <28°C | Coma, hypotension, acidemia, VFib, asystole, flaccidity, apnea |

### Re-warming Options

- gentle fluid and electrolyte replacement in all (due to cold diuresis)
- **passive external re-warming**
  - suitable for most stable patients with core temperature >32.2°C
  - involves covering patient with insulating blanket; body generates heat and re-warms through metabolic process, shivering

- **active external re-warming**
  - involves use of warming blankets
  - beware of "afterdrop" phenomenon
  - safer when done in conjunction with active core re-warming
- **active core re-warming**
  - generally for patients with core temperature <32.2°C, and/or with cardiovascular instability
  - avoids "afterdrop" seen with AER alone
  - re-warm core by using
    - warmed humidified oxygen, IV fluids
    - peritoneal dialysis with warm fluids
    - gastric/colonic/pleural irrigation with warm fluids
    - external circulation (cardiopulmonary bypass machine) is most effective and fastest

### Approach to Cardiac Arrest in the Hypothermic Patient

- do all procedures gently or may precipitate VFib
- check pulse and rhythm for at least 1 min; may have profound bradycardia
- if any pulse at all (even very slow) do NOT do CPR
- if in VFib try to defibrillate up to maximum 3 shocks if core temperature <30°C
- intubate if required, ventilate with warmed, humidified $O_2$
- medications (vasopressors, antidysrhythmics) may not be effective at low temperatures controversial; may try one dose
- focus of treatment is re-warming

## FROSTBITE

### Classification

- ice crystals form between cells
- classified according to depth – similar to burns (1st to 3rd degree)
- 1st degree
  - symptoms: initial paresthesia, pruritus
  - signs: erythema, edema, hyperemia, no blisters
- 2nd degree
  - symptoms: numbness
  - signs: blistering (clear), erythema, edema
- 3rd degree
  - symptoms: pain, burning, throbbing (on thawing); may be painless if severe
  - signs: hemorrhagic blisters, skin necrosis, edema, no movement
- 4th degree
  - extension into subcuticular, osseous, and muscle tissues

### Management

- treat for hypothermia: $O_2$, IV fluids, maintenance of body warmth
- remove wet and constrictive clothing
- immerse in 40-42°C agitated water for 10-30 min (very painful; administer adequate analgesia)
- clean injured area and leave it open to air
- consider aspiration/debridement of blisters (controversial)
- debride skin
- tetanus prophylaxis
- consider penicillin G as frost bite injury has high risk of infection
- surgical intervention may be required to release restrictive eschars
- never allow a thawed area to re-chill/freeze

# Burns

- see Plastic Surgery, PL18

### Clinical Feature/Physical Exam Findings

- burn size
  - rule of nines; does not include 1st degree burns
- burn depth
  - superficial (1st degree): epidermis only (e.g. sunburn), painful and tender to palpation
  - superficial partial thickness (2nd degree): extends to epidermis and superficial dermis, blister formation occurs, very painful
  - deep partial thickness (2nd degree): involves hair follicles, sebaceous glands; skin is blistered, exposed dermis is white to yellow, absent sensation
  - full thickness (3rd degree): epidermis and all dermal layers; skin is pale, insensate, and charred or leathery
  - deep (4th degree): involvement of fat, muscle, even bone

### Management

- remove noxious agent/stop burning process
- establish airway if needed (indicated with burns >40% BSA or smoke inhalation injury)
- resuscitation for 2nd and 3rd degree burns (after initiation of 2 large bore IVs)

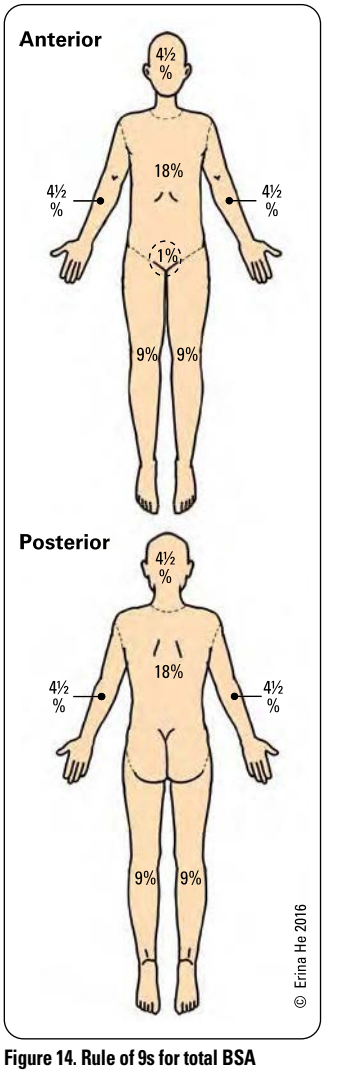



**Figure 14. Rule of 9s for total BSA**

- fluid boluses if unstable
  - Parkland Formula: Ringer's lactate 4 cc/kg/%BSA burned; give half in first 8 h, half in next 16 h; maintenance fluids are also required if patient cannot tolerate PO hydration
  - urine output is best measure of resuscitation, should be 40-50 cc/h or 0.5 cc/kg/h; avoid diuretics
- pain relief: continuous morphine infusion with breakthrough bolus
- investigations: CBC, electrolytes, U/A, CXR, ECG, ABG, carboxyhemoglobin
- burn wound care: prevent infection, clean/debride with mild soap and water, sterile dressings
- escharotomy or fasciotomy for circumferential burns (chest, extremities)
- topical antibiotics, burn victims are highly susceptible to infection (portal of entry with reduced immune function) – systemic antibiotics are often required
- tetanus prophylaxis if burn is deeper than superficial dermis



Use palm of the patient's hand to estimate 1% of BSA affected

### Disposition
- admit
  - 2nd degree burns >10% BSA, or any significant 3rd degree burns
  - 2nd degree burns on face, hands, feet, perineum, or across major joints
  - electrical, chemical burns, and inhalation injury
  - burn victims with chronic medical conditions or immunosuppressed patients



**Burn Causes**
- Thermal (flame, scald)
- Chemical
- Radiation (UV, medical/therapeutic)
- Electrical

## Inhalation Injury

### Etiology
- carbon monoxide or cyanide poisoning
- direct thermal injury: limited to upper airway (above the vocal cords)
- smoke causes bronchospasm and edema from particulate matter and toxic inhalants (tissue asphyxiates, pulmonary irritants, systemic toxins)



Always look for inhalational injury in patients with burns. Intubate early if you suspect inhalation injury, as airway can become obstructed due to edema

### History and Physical Exam
- risk factors: closed space fires, period of unconsciousness, noxious chemicals involved
- cherry red skin (unreliable, usually post-mortem finding)
- singed nasal hairs, soot on oral/nasal membranes, sooty sputum
- hoarseness, stridor, dyspnea
- decreased LOC, confusion
- $PO_2$ normal but $O_2$ saturation low suggests CO poisoning

### Investigations
- measure carboxyhemoglobin levels, co-oximetry
- ABG
- CXR ± bronchoscopy

### Management
- CO poisoning: 100% $O_2$ ± hyperbaric $O_2$ (controversial)
- direct thermal injury: humidified oxygen, early intubation, pulmonary toilet, bronchodilators, and mucolytics (N-acetylcysteine)

## Bites

### MAMMALIAN BITES
- see Plastic Surgery, PL11

### History
- time and circumstances of bite, symptoms, allergies, tetanus immunization status, comorbid conditions, risk of rabies exposure/transmission, HIV/hepatitis risk (human bite)
- high morbidity associated with clenched fist injuries, "fight bites"

### Physical Exam
- assess type of wound: abrasion, laceration, puncture, crush injury
- assess for direct tissue damage: skin, bone, tendon, neurovascular status

### Investigations
- if bony injury or infection suspected, check for fracture and gas in tissue with x-rays
- get skull films in children with scalp bite wounds ± CT to rule out cranial perforation
- ultrasound may be helpful for identifying abscess formation as well as locating radiolucent foreign bodies in infected wounds

### Initial Management
- wound cleaning and copious irrigation as soon as possible
- irrigate/debride puncture wounds if feasible, but not if sealed or very small openings; avoid hydrodissection along tissue planes
- debridement is important in crush injuries to reduce infection and optimize cosmetic and functional repair

- culture wound if signs of infection (erythema, necrosis, or pus); obtain anaerobic cultures if wound foul smelling, necrotizing, or abscess; notify lab that sample is from bite wound
- suturing
  - vascular structures (i.e. face and scalp) are less likely to become infected, therefore consider suturing
  - allow avascular structures (i.e. pretibial regions, hands, and feet) to heal by secondary intention
- tetanus immunization if >10 yr or incomplete primary series

### Prophylactic Antibiotics

- types of infections resulting from bites: cellulitis, lymphangitis, abscesses, tenosynovitis, osteomyelitis, septic arthritis, sepsis, endocarditis, meningitis
- a 3-5 d course of antibiotics is recommended for all bite wounds to the hand and should be considered in other bites if any high-risk factors present
- dog and cat bites (pathogens: Pasteurella multocida, S. aureus, S. viridans)
  - 10-50% of cat bites, 5% of dog bites become infected
  - 1st line: amoxicillin + clavulanic acid
- human bites (pathogens: Eikenella corrodens, S. aureus, S. viridans, oral anaerobes)
  - 1st line: amoxicillin + clavulanic acid
- rabies (see Infectious Diseases, ID18)
  - reservoirs: warm-blooded animals except rodents, lagomorphs (e.g. rabbits)
  - post-exposure vaccine is effective; treatment depends on local prevalence

### INSECT BITES

- bee stings
  - 5 types of reactions to stings (local, large local, systemic, toxic, unusual)
  - history and physical exam key to diagnosis; no lab test will confirm
  - investigations: CBC, electrolytes, BUN, Cr, glucose, ABGs, ECG
  - ABC management, epinephrine 0.1 mg IV over 5 min if shock, antihistamines, cimetidine 300 mg IV/IM/PO, steroids, β-agonists for SOB/wheezing 3 mg in 5 mL NS via nebulizer, local site management
- West Nile virus (see Infectious Diseases, ID22)

## Near Drowning

- most common in children <4 yr and teenagers
- causes lung damage, hypoxemia, and may lead to hypoxic encephalopathy
- must also assess for shock, C-spine injuries, hypothermia, and scuba-related injuries (barotrauma, air emboli, lung re-expansion injury)
- complications: volume shifts, electrolyte abnormalities, hemolysis, rhabdomyolysis, renal, DIC

### Physical Exam

- ABCs, vitals: watch closely for hypotension
- respiratory: rales (ARDS, pulmonary edema), decreased breath sounds (pneumothorax)
- CVS: murmurs, dysrhythmias, JVP (CHF, pneumothorax)
- H&N: assess for C-spine injuries
- neurological: GCS or AVPU, pupils, focal deficits

### Investigations

- labs: CBC, electrolytes, ABGs, Cr, BUN, INR, PTT, U/A (drug screen, myoglobin)
- imaging: CXR (pulmonary edema, pneumothorax) ± C-spine imaging
- ECG

### Management

- ABCs, treat for trauma, shock, hypothermia
- cardiac and $O_2$ monitors, IV access
- intensive respiratory care
  - ventilator assistance if decreased respirations, $pCO_2$ >50 mmHg, or $pO_2$ <60 mmHg on maximum $O_2$
  - may require intubation for airway protection, ventilation, pulmonary toilet
  - high flow $O_2$/CPAP/BiPAP may be adequate but some may need mechanical ventilation with positive end-expiratory pressure
- dysrhythmias: usually respond to corrections of hypoxemia, hypothermia, and acidosis
- vomiting: very common, NG suction to avoid aspiration
- convulsions: usually respond to $O_2$; if not, diazepam 5-10 mg IV slowly
- bronchospasm: bronchodilators
- bacterial pneumonia: prophylactic antibiotics not necessary unless contaminated water or hot tub (*Pseudomonas*)
- always initiate CPR in drowning-induced cardiac arrest even if patient hypothermic; continue CPR until patient is fully rewarmed

### Disposition

- non-significant submersion: discharge after short observation
- significant submersion (even if asymptomatic): long period of observation (72 h) as pulmonary edema may appear late
- CNS symptoms or hypoxemia: admit
- severe hypoxemia, decreased LOC: ICU



"Secondary drowning" where the onset of symptoms, as a result of pulmonary edema or infection, can be insidious, developing over hours, or possibly even days, must be anticipated in the near drowning patient

# Toxicology

## "ABCD$_3$EFG" of Toxicology

- basic axiom of care is symptomatic and supportive treatment
- address underlying problem only once patient is stable

**A** **A**irway (consider stabilizing C-spine)
**B** **B**reathing
**C** **C**irculation
**D1** **D**rugs
  - ACLS as necessary to resuscitate the patient
  - universal antidotes

**D2** **D**raw bloods
**D3** **D**econtamination (decrease absorption)
**E** **E**xpose (look for specific toxidromes)/Examine the patient
**F** **F**ull vitals, ECG monitor, Foley, X-rays
**G** **G**ive specific antidotes and treatments

- reassess
- call Poison Information Centre
- obtain corroborative history from family, bystanders

**Principles of Toxicology**
4 principles to consider with all ingestions:
- Resuscitation (ABCD$_3$EFG)
- Screening (toxidrome? clinical clues?)
- Decrease absorption of drug
- Increase elimination of drug

## D1 – Universal Antidotes

- treatments that will not harm patients and may be essential

### Dextrose (glucose)
- give to any patient presenting with altered LOC
- measure blood glucose prior to glucose administration if possible
- adults: 0.5-1.0 g/kg (1-2 mL/kg) IV of D50W
- children: 0.25 g/kg (2-4 mL/kg) IV of D25W

### Oxygen
- do not deprive a hypoxic patient of oxygen no matter what the antecedent medical history (i.e. even COPD with $CO_2$ retention)
- if depression of hypoxic drive, intubate and ventilate
- exception: paraquat or diquat (herbicides) inhalation or ingestion (oxygen radicals increase morbidity)

### Naloxone (central μ-receptor competitive antagonist, shorter t1/2 than naltrexone)
- antidote for opioids: administration is both diagnostic and therapeutic (1 min onset of action)
- used for the undifferentiated comatose patient
- loading dose
  - adults
    - response to naloxone can be drastic, so stepwise delivery of initial 2 mg bolus is recommended
    - draw up 2 mg to deliver IV/IM/SL/SC or via ETT (ETT dose = 2-2.5x IV dose)
      - 1st dose 0.4 mg (for a chronic opioid user, the initial dose may be much smaller)
      - if no response, deliver second dose 0.6 mg
      - if still no response, deliver remaining 1 mg
  - child
    - 0.01 mg/kg initial bolus IV/IO/ETT (max 2mg per dose)
    - children over 20 kg can receive naloxone 2 mg IV
  - maintenance dose
    - may be required because half-life of naloxone (30-80 min) is much shorter than many opioids
    - hourly infusion rate at 2/3 of initial dose that allowed patient to be roused

### Thiamine (Vitamin B1)
- 100 mg IV/IM with IV/PO glucose to all patients
- given to prevent/treat Wernicke's encephalopathy
- a necessary cofactor for glucose metabolism (may worsen Wernicke's encephalopathy if glucose given before thiamine), but do not delay glucose if thiamine unavailable
- must assume all undifferentiated comatose patients are at risk

**Universal Antidotes**

**DONT**
**D**extrose
**O**xygen
**N**aloxone
**T**hiamine (must give BEFORE dextrose)

Administration of naloxone can cause opioid withdrawal in chronic users:
**Minor** withdrawal may present as lacrimation, rhinorrhea, diaphoresis, yawning, piloerection, HTN, and tachycardia
**Severe** withdrawal may present as hot and cold flashes, arthralgias, myalgias, N/V, and abdominal cramps

Thiamine is deficient in the malnourished. Consider in patients with alcohol use disorder, anorexia, or malnutrition states

# D2 – Draw Bloods

- essential tests
  - CBC, electrolytes, BUN/Cr, glucose, INR/PTT, osmolality
  - ABGs, $O_2$ sat
  - ASA, acetaminophen, EtOH levels
- potentially useful tests
  - drug levels – this is NOT a serum drug screen
  - $Ca^{2+}$, $Mg^{2+}$, $PO_4^{3-}$
  - protein, albumin, lactate, ketones, liver enzymes, CK – depending on drug and clinical feature

## Serum Drug Levels

- treat the patient, not the drug level
- negative toxicology screen does not rule out a toxic ingestion – signifies only that the specific drugs tested were not detectable in the specimen
- specific drugs available on general screen vary by institution; check before ordering
- urine screens also available (qualitative only; not often thought to change management)



Urine drug screen is costly and generally not helpful in the ED management of the poisoned patient

### Table 30. Toxic Gaps (see Nephrology, NP16)

**METABOLIC ACIDOSIS**

**Increased AG**: "**GOLDMARK**" (* = toxic)
**G**lycols* (ethylene glycol, propylene glycol)
**O**xoproline (metabolite of acetaminophen)*
**L**-lactate
**D**-lactate (acetaminophen, short bowel syndrome, propylene glycol infusions for lorazepam & phenobarbital)
**M**ethanol*
**A**SA*
**R**enal failure
**K**etoacidosis (DKA, EtOH*, starvation)

**Increased osmolar gap: "MAE DIE"** (if it ends in "-ol", it will likely increase the osmolar gap)
**M**ethanol
**A**cetone
**E**thanol
**D**iuretics (glycerol, mannitol, sorbitol)
**I**sopropanol
**E**thylene glycol

Note: normal osmolar gap does not rule out toxic alcohol; only an elevated gap is helpful

**Decreased AG**
Electrolyte imbalance (increased $Na^+/K^+/Mg^{2+}$)
Hypoalbuminemia (50% fall in albumin ~5.5 mmol/L decrease in the AG)
Lithium, bromine elevation
Paraproteins (multiple myeloma)

**Increased $O_2$ saturation gap**
Carboxyhemoglobin
Methemoglobin
Sulfmethemoglobin

**Normal AG**
Renal HCO3- loss: renal tubular acidosis, hyperparathyroidism
GI HCO3- loss: diarrhea, fistula
Other: NS infusion, acetazolamide, hyperkalemia, hypoaldosteronism



**Anion Gap**
$= Na^+ - Cl^- - HCO_3^-$
Normal AG ≤12 mM/L

### Table 31. Use of the Clinical Laboratory in the Initial Diagnosis of Poisoning

| Test | Finding | Selected Causes |
|---|---|---|
| **ABG** | Hypoventilation (high $pCO_2$) | CNS depressants (opioids, sedative-hypnotic agents, phenothiazines, EtOH) |
| | Hyperventilation (low $pCO_2$) | Salicylates, CO, other asphyxiants |
| **Electrolytes** | AG metabolic acidosis | "**GOLDMARK**": see Table 30 |
| | Hyperkalemia | Digitalis glycosides, fluoride, potassium |
| | Hypokalemia | Theophylline, caffeine, β-adrenergic agents, soluble barium salts, diuretics, insulin |
| **Glucose** | Hypoglycemia | Oral hypoglycemic agents, insulin, EtOH, ASA |
| **Osmolality and Osmolar Gap** | Elevated osmolar gap | "**MAE DIE**": see Table 30 |
| **ECG** | Wide QRS complex | TCAs, quinidine, other class Ia and Ic antidysrhythmic agents |
| | Prolonged QT interval | Terfenadine, astemizole, antipsychotics |
| | Atrioventricular block | $Ca^{2+}$ antagonists, digitalis glycosides, phenylpropanolamine |
| **Abdominal X-Ray** | Radioopaque pills or objects | "**CHIPES**": **C**alcium, **C**hloral hydrate, **C**$Cl_4$, **H**eavy metals, **I**ron, **P**otassium, **E**nteric coated **S**alicylates, and some foreign bodies |
| **Serum Acetaminophen** | Elevated level (>140 mg/L or 1000 µmol/L 4 h after ingestion) | May be only sign of acetaminophen poisoning |

# D3 – Decontamination and Enhanced Elimination

## Ocular Decontamination
- saline irrigation to neutralize pH; alkali exposure requires ophthalmology consult

## Dermal Decontamination (Wear Protective Gear)
- remove clothing, brush off toxic agents, irrigate all external surfaces

## Gastrointestinal Decontamination
- single dose activated charcoal
  - use of activated charcoal is a source of much debate amongst toxicologists. Evidence of effectiveness is not strong, and risk of aspiration is high.
  - adsorption of drug/toxin to activated charcoal decreases toxin bioavailability
  - contraindications: unprotected airway, late presentation after ingestion, small bowel obstruction, poor toxin adsorption
  - dose: 10 g/g drug ingested or 1g/kg body weight (may vary depending on ingestion)
  - odourless, tasteless, prepared as slurry with $H_2O$
- whole bowel irrigation (very rarely used)
  - 500 mL/h (child) to 2000 mL/h (adult) of polyethylene glycol solution by mouth until clear effluent per rectum
    - start slow (500 mL in an adult) and aim to increase rate hourly as tolerated
  - indications
    - awake, alert, can be nursed upright OR intubated and airway protected
    - delayed release product
    - drug/toxin not bound to charcoal
    - drug packages (if any evidence of breakage emergency surgery)
    - recent toxin ingestion
  - contraindications
    - evidence of ileus, perforation, or obstruction
- multidose activated charcoal
  - may be used for: carbamazepine, phenobarbital, quinine, theophylline for toxins which undergo enterohepatic recirculation
  - removes drug that has already been absorbed by drawing it back into GI tract
  - various regimens: 12.5 g (1/4 bottle) PO q1h or 25 g (1/2 bottle) PO q2h until non-toxic
- surgical removal in extreme cases
  - surgical indicated for drugs that are toxic, form concretions, or cannot be removed by conventional means
- use of cathartics (i.e. ipecac) and gastric lavage in the ED is not recommended

## Lipid Emulsification
- new therapy used in cardiogenic shock due to toxins
- may be used for: anesthetics, β-blocker and calcium channel blocker overdose
- initial bolus 1.5mL/kg 20% lipid solution over 2-3 min then infusion of 0.25mL/kg/min

## Urine Alkalinization
- may be used for: ASA, methotrexate, phenobarbital, chlorpropamide
- weakly acidic substances can be trapped in alkali urine (pH >7.5) to increase elimination

## Hemodialysis
- indications/criteria for hemodialysis
  - toxins that have high water solubility, low protein binding, low molecular weight, adequate concentration gradient, small volume of distribution, or rapid plasma equilibration
  - clinical deterioration despite maximal medical support
- useful for the following toxins
  - methanol
  - ethylene glycol
  - salicylates
  - lithium
  - phenobarbital
  - chloral hydrate ( trichloroethanol)
- others include theophylline, carbamazepine, valproate, methotrexate

# E – Expose and Examine the Patient

- vital signs (including temperature), skin (needle tracks, colour), mucous membranes, pupils, odours, and CNS
- head-to-toe survey including
  - C-spine
  - signs of trauma, seizures (incontinence, "tongue biting", etc.), infection (meningismus), or chronic alcohol/drug misuse (track marks, nasal septum erosion)
  - feel the patient's axillae; in the average patient, should be somewhat moist (if dry, may indicate anticholinergic toxicity)
- mental status

**Table 32. Specific Toxidromes**

| Toxidrome | Overdose Signs and Symptoms | | Examples of Drugs |
|---|---|---|---|
| **Anticholinergic** | Hyperthermia<br>Dilated pupils<br>Dry skin<br>Vasodilation<br>Agitation/hallucinations<br>Ileus<br>Urinary retention<br>Tachycardia | "Hot as a hare"<br>"Blind as a bat"<br>"Dry as a bone"<br>"Red as a beet"<br>"Mad as a hatter"<br>"The bowel and bladder lose their tone and the heart goes on alone" | Antidepressants (e.g. TCAs)<br>Cyclobenzaprine (Flexeril®)<br>Carbamazepine<br>Antihistamines (e.g. diphenhydramine)<br>Antiparkinsonians<br>Antipsychotics<br>Antispasmodics<br>Belladonna alkaloids (e.g. atropine) |
| **Cholinergic** | **"DUMBELS"**<br>**D**iaphoresis, **D**iarrhea, **D**ecreased BP<br>**U**rination<br>**M**iosis<br>**B**ronchospasm, **B**ronchorrhea, **B**radycardia<br>**E**mesis, **E**xcitation of skeletal muscle<br>**L**acrimation<br>**S**alivation, **S**eizures | | Natural plants: mushrooms, trumpet flower<br>Anticholinesterases: physostigmine<br>Insecticides (organophosphates, carbamates)<br>Nerve gases |
| **Extrapyramidal** | Dysphonia, dysphagia<br>Rigidity and tremor<br>Motor restlessness, crawling sensation (akathisia)<br>Constant movements (dyskinesia)<br>Dystonia (muscle spasms, laryngospasm, trismus, oculogyric crisis, torticollis) | | Major tranquilizers<br>Antipsychotics |
| **Hemoglobin Derangements** | Increased respiratory rate<br>Decreased LOC<br>Seizures<br>Cyanosis unresponsive to $O_2$<br>Lactic acidosis | | CO poisoning (carboxyhemoglobin)<br>Drug ingestion (methemoglobin, sulfmethemoglobin) |
| **Opioid, Sedative/ Hypnotic, EtOH** | Hypothermia<br>Hypotension<br>Respiratory depression<br>Dilated or constricted pupils (pinpoint in opioid)<br>CNS depression | | EtOH<br>Benzodiazepines<br>Opioids (morphine, heroin, fentanyl, etc.)<br>Barbiturates<br>GHB ("G," "liquid gold") |
| **Sympathomimetic** | Increased temperature<br>CNS excitation (including seizures)<br>Tachycardia, HTN<br>N/V<br>Diaphoresis<br>Dilated pupils | | Amphetamines, caffeine, cocaine, LSD, phencyclidine<br>Ephedrine and other decongestants<br>Thyroid hormone<br>Sedative or EtOH withdrawal |
| **Serotonin Syndrome** | Mental status changes, autonomic hyperactivity, neuromuscular abnormalities, hyperthermia, diarrhea, HTN | | MAOI, TCA, SSRI, opiate analgesics<br>Cough medicine, weight reduction medications |

Note: ASA poisoning and hypoglycemia mimic sympathomimetic toxidrome

# F – Full Vitals, ECG Monitor, Foley, X-Rays

# G – Give Specific Antidotes and Treatments

### Urine Alkalinization Treatment for ASA Overdose

- urine pH >7.5
- fluid resuscitate first, then 3 amps $NaHCO_3$/L of D5W at 1.5x maintenance
- add 20-40 mEq/L KCl if patient is able to urinate

### Table 33. Protocol for Warfarin Overdose

| INR | **Management**: Consider Prothrombin Complex Concentrate (Octaplex®, Beriplex®) for any elevated INR, AND either life-threatening bleeding, or a plan for the patient to undergo a surgical procedure within the next 6 h |
|---|---|
| **<5.0** | Cessation of warfarin administration, observation, serial INR/PT |
| **5.1–9.0** | If no risk factors for bleeding, hold warfarin x 1-2 d and reduce maintenance dose<br>OR<br>Vitamin K 1-2 mg PO if patient at increased risk of bleeding |
| **9.1–20.0** | Hold warfarin, vitamin K 2-4 mg PO, serial INR/PT, additional vitamin K if necessary |
| **>20.0** | Hold warfarin, vitamin K 10 mg IV over 10 min, increase vitamin K dosing (q4h) if needed |

### Table 34. Specific Antidotes and Treatments for Common Toxins*

| Toxin | Treatment | Considerations |
|---|---|---|
| **Acetaminophen** | Decontaminate (activated charcoal)<br>N-acetylcysteine | Often clinically silent; evidence of liver/renal damage delayed >24 h<br>Toxic dose >200 mg/kg (>7.5 g adult)<br>Monitor drug level 4 h post-ingestion; also liver enzymes, INR, PTT, BUN, Cr<br>Hypoglycemia, metabolic acidosis, encephalopathy poor prognosis<br>Dialysis may be required to manage in very high overdoses |
| **Acute Dystonic Reaction** | Benztropine: 1-2 mg IM/IV then 2 mg PO x 3 d<br>OR Diphenhydramine 1-2 mg/kg IV,<br>then 25 mg PO qid x 3 d | Benztropine (Cogentin®) has euphoric effect and the potential for misuse |
| **Anticholinergics** | Consider decontamination (activated charcoal)<br>Supportive care | Special antidotes available; consult Poison Information Centre |
| **ASA** | Consider decontamination (activated charcoal)<br>Alkalinize urine; want urine pH >7.5 | Monitor serum pH and drug levels closely<br>Monitor $K^+$ level; may require supplement for urine alkalinization<br>Hemodialysis may be needed if intractable metabolic acidosis, very high levels, or end-organ damage (i.e. unable to diurese) |
| **Benzodiazepines** | Consider decontamination (activated charcoal)<br>Flumazenil<br>Supportive care | |
| **β-blockers** | Consider decontamination (activated charcoal, consider whole bowel irrigation for extended-release ingestion)<br>IV glucagon, IV calcium chloride, IV high-dose insulin (with dextrose), IV intralipid | |
| **Calcium Channel Blockers** | Consider decontamination (activated charcoal, consider whole bowel irrigation for extended-release ingestion)<br>IV glucagon, IV calcium chloride, IV high-dose insulin (with dextrose), IV intralipid | Order ECG, electrolytes (especially $Ca^{2+}$, $Mg^{2+}$, $Na^+$, $K^+$) |
| **Cocaine** | Decontaminate (activated charcoal) if oral<br>Aggressive supportive care | β-blockers are contraindicated in acute cocaine toxicity<br>Intralipid for life-threatening symptoms |
| **CO Poisoning** | See *Inhalation Injury*, ER47<br>Supportive care<br>100% $O_2$ ; may require hyperbaric $O_2$ | Order ECG, VBG. Consider lactate and troponin depending on specific presentation |
| **Cyanide** | Hydroxocobalamin | |
| **Digoxin** | Consider decontamination (activated charcoal)<br>Digoxin-specific Ab fragments<br>10-20 vials IV if acute; 3-6 if chronic<br>1 vial (40 mg) neutralizes 0.5 mg of toxin | Use for life-threatening dysrhythmias unresponsive to conventional therapy, 6 h serum digoxin >12 nmol/L, initial $K^+$ >5 mmol/L, ingestion >10 mg (adult)/>4 mg (child)<br>Common dysrhythmias include VFib, VTach, and conduction blocks |
| **Ethanol** | Thiamine 100 mg IM/IV<br>Manage airway and circulatory support | Mouthwash = 70% EtOH; perfumes and colognes = 40-60% EtOH<br>Order serum EtOH level and glucose level; treat glucose level appropriately |
| **Ethylene Glycol/ Methanol** | Fomepizole (4-methylpyrazole)<br>15 mg/kg IV load over 30 min,<br>then 10 mg/kg q12h OR<br>Ethanol (10%) 10 mL/kg over 30 min, then 1.5 mL/h | CBC, electrolytes, glucose, ethanol level<br>Consider hemodialysis |
| **Heparin** | Protamine sulfate 25-50 mg IV | For unfractionated heparin overdose only |
| **Insulin IM/SC/ Oral Hypoglycemic** | Glucose IV/PO/NG tube<br>Glucagon: 1-2 mg IM (if no access to glucose) | Glyburide carries highest risk of hypoglycemia among oral agents<br>Consider octreotide for oral hypoglycemics (50-100 μg SC q6h) in these cases; consult local Poison Information Centre |
| **MDMA** | Consider decontamination (activated charcoal)<br>Supportive care | Monitor CK; treat rhabdomyolysis with high flow fluids: aggressive external cooling for hyperthermia<br>Review medical history if possible for serotonergic use |
| **Opioids** | See *Universal Antidotes*, ER49 | |
| **TCAs** | Consider decontamination (activated charcoal)<br>Aggressive supportive care<br>$NaHCO_3$ bolus for wide QRS/seizures | Flumazenil antidote contraindicated in combined TCA and benzodiazepine overdose<br>Also consider cardiac and hypotension support, seizure control<br>Intralipid therapy |

* Call local Poison Information Centre for reporting of cases, specific doses, and treatment recommendations. Most toxicology cases should involve communication with your local Poison Information Centre.

# Alcohol Related Emergencies

- see Psychiatry, PS26

## Acute Intoxication

- slurred speech, CNS depression, disinhibition, lack of coordination
- nystagmus, diplopia, dysarthria, ataxia, may progress to coma
- hypotension (peripheral vasodilation)
- if obtunded, rule out
  - head trauma/intracranial hemorrhage
  - associated depressants, toxic alcohols
- may also contribute to respiratory/cardiac depression
  - hypoglycemia (screen with bedside glucometer)
  - hepatic encephalopathy: confusion, altered LOC, coma
- precipitating factors: GI bleed, infection, sedation, electrolyte abnormalities, protein meal
  - Wernicke's encephalopathy (ataxia, ophthalmoplegia, delirium)
  - post-ictal state, basilar stroke

Alcohol levels correlate poorly with intoxication

Alcohol intoxication may invalidate informed consent

## Withdrawal

- beware of withdrawal signs
- treatment
  - diazepam 10-20 mg IV/PO or lorazepam 2-4 mg IV/PO q1h until calm
- frequency of dosing may have to be increased depending on clinical response
  - may use CIWA protocol and give benzodiazepines as above until CIWA <10
  - thiamine 100 mg IM/IV then 50-100 mg/d
  - magnesium sulfate 4 g IV over 1-2 h (if hypomagnesemic)
  - admit patients with delirium tremens or multiple seizures

**CIWA Withdrawal Symptoms**
- N/V
- Tremor
- Paroxysmal sweats
- Anxiety
- Agitation
- Visual disturbances
- Tactile disturbances
- Auditory disturbances
- Headache
- Disorientation

10 symptoms each scored out of 7 except orientation, which is scored out of 4

**Table 35. Alcohol Withdrawal Signs**

| Time Since Last Drink | Syndrome | Description |
|---|---|---|
| **6-8 h** | Mild withdrawal | Generalized tremor, anxiety, agitation, but no delirium<br>Autonomic hyperactivity (sinus tachycardia), insomnia, N/V |
| **1-2 d** | Alcoholic hallucinations | Visual (most common), auditory, and tactile hallucinations<br>Vitals often normal |
| **8 h-2 d** | Withdrawal seizures | Typically brief generalized tonic-clonic seizures<br>May have several within a few hours<br>CT head if focal seizures have occurred |
| **3-5 d** | DT | 5% of untreated withdrawal patients<br>Severely confused state, fluctuating LOC<br>Agitation, insomnia, hallucinations/delusions, tremor<br>Tachycardia, hyperpyrexia, diaphoresis<br>High mortality rate |

## Cardiovascular Complications

- HTN
- cardiomyopathy: SOB, edema
- dysrhythmias ("holiday heart")
- AFib (most common), atrial flutter, SVT, VTach (especially Torsades if hypomagnesemic/hypokalemic)

## Metabolic Abnormalities

- alcoholic ketoacidosis
  - antigen metabolic acidosis, urine ketones, low glucose, and normal osmolality
  - history of chronic alcohol intake with abrupt decrease/cessation
  - malnourished, abdominal pain with N/V
  - treatment: dextrose, thiamine (100 mg IM/IV prior to dextrose), volume repletion (with NS)
  - generally resolves in 12-24 h
- other alcohols
  - ethylene glycol: CNS, CVS, renal findings
  - methanol
    - early: lethargy, confusion
    - late: headache, visual changes, N/V, abdominal pain, tachypnea
  - both ethylene glycol and methanol produce severe metabolic acidosis with anion gap (as the alcohol is metabolized) and osmolar gap (initially after ingestion but before metabolism)
  - EtOH co-ingestion is protective

  - treatment
    - urgent hemodialysis required
    - fomepizole 15 mg/kg IV bolus (treatment of choice) or EtOH 10% IV bolus and infusion to achieve blood level of 22 mmol/L (EtOH loading may be done PO)
    - consider folic acid for methanol, and pyridoxine and thiamine for ethylene glycol – both help reduce conversion to active metabolites
- other abnormalities associated with alcohol: hypomagnesemia, hypophosphatemia, hypocalcemia, hypoglycemia, hypokalemia

### Gastrointestinal Abnormalities
- gastritis
  - common cause of abdominal pain and GI bleed in chronic alcohol users
- pancreatitis
  - serum amylase very unreliable in patients with chronic pancreatitis, may need serum lipase
  - hemorrhagic form (15%) associated with increased mortality
  - fluid resuscitation very important
- hepatitis
  - AST/ALT ratio >2 suggests alcohol as the cause as well as elevated GGT with acute ingestion
- peritonitis/spontaneous bacterial peritonitis
  - leukocytosis, fever, generalized abdominal pain/tenderness
  - occasionally accompanies cirrhosis
  - paracentesis for diagnosis (common pathogens: E. coli, Klebsiella, Streptococcus)
  - albumin shown to improve outcomes in SBP patients
- GI bleeds
  - most commonly gastritis or ulcers, even if patient known to have varices
  - consider Mallory-Weiss tear secondary to retching
  - often complicated by underlying coagulopathies
  - minor: treat with antacids
  - severe or recurrent: endoscopy

### Disposition
- before patient leaves ED ensure stable vital signs, can walk unassisted, and fully oriented
- offer social services to find shelter or detox program
- ensure patient can obtain any medications prescribed and can complete any necessary follow-up

## Approach to the Overdose Patient



**Indications to Suspect Overdose**
- Altered LOC/coma
- Young patient with life-threatening dysrhythmia
- Trauma patient
- Bizarre or puzzling clinical feature

### History
- age, weight, underlying medical problems, medications
- substance, route, and quantity
- time and symptoms since exposure determines prognosis and need for decontamination
- route
- intention, suicidality

### Physical Exam
- focus on: ABCs, LOC/GCS, vitals, pupils

### Disposition from the Emergency Department
- methanol, ethylene glycol
  - delayed onset, admit, and watch clinical and biochemical markers
- TCAs
  - prolonged/delayed cardiotoxicity warrants admission to monitored ICU bed
  - if asymptomatic and no clinical signs of intoxication: 6 h ED observation adequate with proper decontamination and no ECG abnormalities
  - sinus tachycardia alone (most common finding) with history of overdose warrants observation in ED
- hydrocarbons/smoke inhalation
  - pneumonitis may lag 6-8 h
  - consider observation for repeated clinical and radiographic examination
- ASA, acetaminophen
  - if borderline level, get second level 2-4 h after first
  - for ASA, must have at least 2 measurements showing decreasing toxin serum concentration before discharge (3 levels minimum)
- oral hypoglycemics
  - admit all patients for minimum 24 h if hypoglycemic and 12 h after last octreotide dose
  - observe asymptomatic patient for at least 8 h

### Psychiatric Consultation
- once patient medically cleared, arrange psychiatric intervention if required
- beware – suicidal ideation may not be expressed

# Psychiatric Emergencies

## Approach to Common Psychiatric Presentations

- see Psychiatry, PS2
- before seeing patient, ensure your own safety; have security/police available if necessary

### History

- safety
  - assess suicidality: suicidal ideation (SI), intent, plan, lethal means, past attempts, protective factors
  - assess homicidality: homicidal ideation (HI), access to weapons, intended victim, and history of violence
  - driving and children
  - command hallucinations
- identify current stressors and coping strategies
- mood symptoms: manic, depressive
- anxiety: panic attacks, generalized anxiety, phobias, obsessive-compulsive disorder, post-traumatic stress disorder
- psychotic symptoms: delusions, hallucinations, disorganized speech, disorganized or catatonic behaviour, negative symptoms (affective flattening, alogia, avolition)
- substance use history: most recent use, amount, previous withdrawal reactions
- past psychiatric history, medications, adherence with medications
- medical history: obtain collateral if available

**Key Functions of Emergency Psychiatric Assessment**

- Is the patient medically stable?
- Rule out medical cause
- Is psychiatric consult needed?
- Are there safety issues (SI, HI)?
- Is patient certifiable? (must demonstrate risk [present/past test] and apparent mental illness [future test])

### Physical Exam

- complete physical exam focusing on: vitals, neurological exam, signs of head trauma, signs of drug toxicity, signs of metabolic disorder
- mental status exam: general appearance, behaviour, cooperation, speech, mood and affect, thought content and form, perceptual disturbances, cognition (including MMSE if indicated), judgment, insight, reliability

**Psychiatric Review of Systems**

**MOAPS**
**M**ood
**O**rganic
**A**nxiety
**P**sychosis
**S**afety

### Investigations

- investigations vary with age, established psychiatric diagnosis vs. first presentation, history and physical suggestive of organic cause
- as indicated: blood glucose, urine and serum toxicology screen, pregnancy test, electrolytes, TSH, AST/ALT, bilirubin, serum Cr, BUN, and osmolality
- blood levels of psychiatric medications
- CT head if suspect neurological etiology
- LP if indicated

## Acute Psychosis

### Differential Diagnosis

- primary psychotic disorder (e.g. schizophrenia)
- secondary to medical condition (e.g. delirium)
- drugs: substance intoxication or withdrawal, medications (e.g. steroids, anticholinergics)
- infectious (CNS)
- metabolic (hypoglycemic, hepatic, renal, thyroid)
- structural (hemorrhage, neoplasm)

### Management

- violence prevention
  - remain calm, empathic, and reassuring
  - ensure safety of staff and patients, have extra staff and/or security on hand
  - patients demonstrating escalating agitation or overt violent behaviour may require physical restraint and/or chemical restraint
- treat agitation: whenever possible, offer medication to patients as opposed to administering with force (helps calm and engage patient)
  - benzodiazepines: lorazepam 2 mg PO/IM/SL
  - antipsychotics: olanzapine 5 mg PO, haloperidol 5 mg PO/IM
- treat underlying medical condition
- psychiatry or Crisis Intervention Team consult

# Suicidal Patient

## Epidemiology
- attempted suicide F>M, completed suicide M>F
- second leading cause of death in people <24 yr
- risk is significantly increased in indigenous and LGBTQ Canadians, particularly trans individuals

## Management
- ensure patient safety: close observation, remove potentially dangerous objects from person and room
- assess thoughts (ideation), means, action (preparatory, practice attempts), previous attempts, protective factors
- admit if there is evidence of active intent and organized plan, access to lethal means, psychiatric disorder, intoxication (suicidal ideation may resolve with few days of abstinence)
- patient may require certification if unwilling to stay voluntarily
- do not start long-term medications in the ED
- psychiatry or Crisis Intervention Team consult

See Psychiatry, *Common Forms*, PS53 for certification (involuntary assessment/admission) considerations

**High Risk Patients**

**SAD PERSONS**
**S**ex = male
**A**ge >45 yr old
**D**epression
**P**revious attempts
**E**thanol use
**R**ational thinking loss
**S**uicide in family
**O**rganized plan
**N**o spouse, no support system
**S**erious illness

# Common Pediatric ED Presentations

# Modified Glasgow Coma Score

**Table 36. Modified GCS**

| Modified GCS for Infants | | |
|---|---|---|
| **Eye Opening** | **Verbal Response** | **Motor Response** |
| 4 – spontaneously | 5 – coos, babbles | 6 – normal, spontaneous movement |
| 3 – to speech | 4 – irritable cry | 5 – withdraws to touch |
| 2 – to pain | 3 – cries to pain | 4 – withdraws to pain |
| 1 – no response | 2 – moans to pain | 3 – decorticate flexion |
| | 1 – no response | 2 – decerebrate extension |
| | | 1 – no response |
| **Modified GCS for Children <4 years** | | |
| **Eye Opening** | **Verbal Response** | **Motor Response** |
| 4 – spontaneously | 5 – oriented, social, speaks, interacts | 6 – normal, spontaneous movement |
| 3 – to speech | 4 – confused speech, disoriented, consolable | 5 – localizes to pain |
| 2 – to pain | 3 – inappropriate words, not consolable/aware | 4 – withdraws to pain |
| 1 – no response | 2 – incomprehensible, agitated, restless, not aware | 3 – decorticate flexion |
| | 1 – no response | 2 – decerebrate extension |
| | | 1 – no response |

Any trauma or suspected trauma patient <1 yr of age with a large, boggy scalp hematoma requires U/S or CT

# Respiratory Distress

- see Pediatrics, P70

## History and Physical Exam
- infants not able to feed, older children not able to speak in full sentences
- anxious, irritable, lethargic – may indicate hypoxia
- tachypnea >60 (>40 if preschool age, >30 if school age), retractions, tracheal tug
  - see Pediatrics, P3 for age specific vital signs
- pulsus paradoxus
- wheezing, grunting, vomiting

**Table 37. Stridorous Upper Airway Diseases: Diagnosis**

| Feature | Croup | Bacterial Tracheitis | Epiglottitis[1] |
|---|---|---|---|
| **Age Range (yr)** | 0.5-4 | 5-10 | 2-8 |
| **Prodrome** | Days | Hours to days | Minutes to hours |
| **Temperature** | Low grade | High | High |
| **Radiography** | Steeple sign | Exudates in trachea | Thumb sign |
| **Etiology** | Parainfluenza | *S. aureus/GAS* | *H. influenzae type b* |
| **Barky Cough** | Yes | Yes | No |
| **Drooling** | Yes | No | Yes |
| **Appear Toxic** | No | Yes | Yes |
| **Intubation/ICU** | No | Yes | Yes |
| **Antibiotics** | No | Yes | Yes |
| **NOTE** | Oral exam | Oral exam | No oral exam, consult ENT |

[1]Now rare with Hib vaccine in common use

### Management
- croup (usually laryngotracheitis caused by parainfluenza viruses)
  - dexamethasone x 1 dose
  - if moderate-severe, add nebulized epinephrine (racemic has limited availability)
  - consider bacterial tracheitis/epiglottitis if unresponsive to croup therapy
  - humidified $O_2$ has no evidence for efficacy
- bacterial tracheitis
  - airway maintenance - usually require intubation, ENT consult, ICU
  - start antibiotics (e.g. cloxacillin), pending C&S
- epiglottitis
  - 4 D's: drooling, dyspnea, dysphagia, dysphonia + tripod sitting
  - do not examine oropharynx or agitate patient
  - immediate anesthesia, ENT call – intubate
  - then IV fluids, antibiotics, blood cultures
- asthma
  - supplemental $O_2$ if saturation <90% or $PaO_2$ <60%
  - bronchodilator therapy: salbutamol (Ventolin®) 0.15 mg/kg x3 by masks q20min
  - give corticosteroid therapy as soon as possible after arrival (prednisolone 2 mg/kg, dexamethasone 0.6 mg/kg, 2 doses 24 h apart)
  - if severe, add 250-500 μg ipratropium (Atrovent®) to first 3 doses salbutamol if critically ill, not responding to inhaled bronchodilators or steroids: give IV bolus, then infusion of MgSO4
  - IV β2-agonists if critically ill and not responding to above

# Febrile Infant and Febrile Seizures

## FEBRILE INFANT
- for fever >38°C without obvious focus
  - <28 d
    - admit
    - full septic workup (CBC and differential, blood C&S, urine C&S, LP ± stool C&S, CXR if indicated)
    - treat empirically with broad spectrum IV antibiotics
  - 28-90 d
    - as above unless infant meets Rochester criteria, partial septic workup (CBC and differential, blood C&S, urine C&S, CXR if indicated)
  - >90 d
    - toxic: admit, treat, full septic workup
    - non-toxic and no focus: investigate as indicated by history and physical

**Rochester Criteria for Febrile Infants Age 28-90 Days Old**
- Non-toxic looking
- Previously well (>37 wk gestational age, home with mother, no hyperbilirubinemia, no prior antibiotics or hospitalizations, no chronic/underlying illness)
- No skin, soft tissue, bone, joint, or ear infection on physical exam
- WBC 5000-15,000, bands <1500, urine <10 WBC/HPF, stool <5 WBC/HPF

## FEBRILE SEIZURES
- see Pediatrics, P78

### Etiology
- children aged 6 mo-6 yr with fever or history of recent fever
- typical vs. atypical febrile seizures
- normal neurological exam afterward
- no evidence of intracranial infection or history of previous non-febrile seizures
- often positive family history of febrile seizures
- relatively well-looking after seizure

### Investigations and Management
- if confirmed febrile seizure: treat fever and look for source of fever
- if not a febrile seizure: treat seizure and look for source of seizure
  - note: may also have fever but may not meet criteria for febrile seizure
- ± EEG (especially if first seizure), head U/S (if fontanelle open)

**Table 38. Typical vs. Atypical Febrile Seizures**

| Characteristic | Typical | Atypical |
|---|---|---|
| **Duration** | <15 min | >15 min |
| **Type of Seizure** | Generalized | Focal features |
| **Frequency** | 1 in 24 h | >1 in 24 h |

# Abdominal Pain

• see Pediatrics, P41

### History
- neuro, infections, autoimmune, hematology, trauma, abuse Hx questions
- nature of pain, associated fever
- associated GI, GU symptoms
- anorexia, decreased fluid intake

### Physical Exam
- HEENT, respiratory, abdominal exam including DRE, testicular/genital exam

**Table 39. Differential Diagnosis of Abdominal Pain in Infants/Children/Adolescents**

| Medical | Surgical |
|---|---|
| Colic | Malrotation with volvulus |
| UTI | Hirschsprung's disease |
| Constipation | Necrotizing enterocolitis |
| Gastroenteritis | Incarcerated hernia |
| Sepsis | Intussusception |
| Henoch-Schönlein purpura | Duodenal atresia |
| IBD | Appendicitis |
| Hemolytic uremic syndrome | Cholecystitis |
| Pneumonia | Pancreatitis |
| Strep throat | Testicular torsion |
| Sickle cell disease crisis | Ectopic pregnancy |
| DKA | Trauma |
| Functional | Pyloric stenosis |

*Remember to keep an index of suspicion for child abuse



**Red Flags for Abdominal Pain**
- Significant weight loss or growth retardation (need growth chart)
- Fever
- Joint pain with objective physical findings
- Rash
- Rectal bleeding
- Rebound tenderness and radiation of pain to back, shoulders, or legs
- Pain wakes from sleep
- Severe diarrhea and encopresis

# Common Infections

• see Pediatrics, P53

**Table 40. Antibiotic Treatment of Pediatric Bacterial Infections**

| Infection | Pathogens | Treatment |
|---|---|---|
| **MENINGITIS SEPSIS** | | |
| **Neonatal** | GBS, *E. coli, Listeria*, Gram-negative bacilli | ampicillin + cefotaxime |
| **1-3 mo** | Same pathogens as above and below | ampicillin + cefotaxime + vancomycin |
| **>3 mo** | *S. pneumoniae, H. influenzae* type b (>5 yr), meningococcus | ceftriaxone + vancomycin |
| **OTITIS MEDIA** | | |
| **1st Line** | *S. pneumoniae, H. influenzae* type b, *M. catarrhalis* | amoxicillin 80-90 mg/kg/d |
| **2nd Line** | | clarithromycin 15 mg/kg/d bid (for penicillin allergy) |
| **Treatment Failure** | | 90 mg/kg/d amoxicillin and 6.4 mg/kg/d clavulanate divided into bid dosage |
| **STREP PHARYNGITIS** | | |
| | Group A β-hemolytic *Streptococcus* | penicillin/amoxicillin or erythromycin (penicillin allergy) |
| **UTI** | | |
| | *E. coli, Proteus, H. influenzae, Pseudomonas, S. saprophyticus, Enterococcus*, GBS | Oral: cephalexin (older children)<br>IV: ampicillin and aminoglycoside |
| **PNEUMONIA** | | |
| **1-3 mo** | Viral, *S. pneumoniae, C. trachomatis, B. pertussis, S. aureus, H. influenzae* | cefuroxime ± macrolide (erythromycin)<br>OR ampicillin ± macrolide |
| **3 mo-5 yr** | Viral, *S. pneumoniae, S. aureus, H. influenzae, Mycoplasma pneumoniae* | ampicillin/amoxicillin or cefuroxime |
| **>5 yr** | As above | ampicillin/amoxicillin + macrolide<br>OR cefuroxime + macrolide |

# Child Abuse and Neglect

- see Pediatrics, P15
- obligation to report any suspected/known case of child abuse or neglect to CAS yourself (do not delegate)
- document injuries
- consider skeletal survey x-rays (especially in non-ambulatory child), ophthalmology consult, CT head
- injury patterns associated with child abuse
  - HI: torn frenulum, dental injuries, bilateral black eyes, traumatic hair loss, diffuse severe CNS injury, retinal hemorrhage
  - Shaken Baby Syndrome: diffuse brain injury, subdural/SAH, retinal hemorrhage, minimal/no evidence of external trauma, associated bony fractures
  - skin injuries: bites, bruises/burns in shape of an object, glove/stocking distribution of burns, bruises of various ages, bruises in protected areas
  - bone injuries: rib fractures without major trauma, femur fractures age <1 yr, spiral fractures of long bones in non-ambulatory children, metaphyseal fractures in infants, multiple fractures of various ages, complex/multiple skull fractures
  - GU/GI injuries: chronic abdominal/perineal pain, injury to genitals/rectum, STI/pregnancy, recurrent vomiting or diarrhea



**Presentation of Neglect**
- Failure to thrive, developmental delay
- Inadequate or dirty clothing, poor hygiene
- Child exhibits poor attachment to parents



**Procedures that may Require Sedation**
- Setting fractures
- Reducing dislocations
- Draining abscesses
- Exploring wounds/ulcers/superficial infections
- Endoscopic examination
- Reduce patient anxiety/agitation for imaging/procedures

# Common Medications

**Table 41. Commonly Used Medications**

| Drug | Dosing Schedule | Indications | Comments |
|---|---|---|---|
| **Acetaminophen** | 325-650 mg PO q4-6h prn | Pain control | Max 4 g daily |
| **Activated charcoal** | 30-100 g PO in 250 mL $H_2O$ | Poisoning/overdose | Efficacy and safety are case-dependent and are a source of debate |
| **ASA** | 325-650 mg PO q4h max 4g/d<br>stroke/MI risk: 81-325 mg PO OD<br>160 mg chewed | Pain control<br>Prevention of adverse cardiac events<br>ACS | |
| **β-blockers (metoprolol)** | 5 mg slow IV q5min x 3 if no contraindications<br>Or<br>25mg PO BID up to 100mg PO BID | Acute MI | |
| **Diazepam** | anxiety: 2-10 mg PO tid/qid<br>alcohol withdrawal: 10-20 mg PO/IV q1h titrated to signs/symptoms | Anxiety<br>Alcohol withdrawal | |
| **Enoxaparin** | 1 mg/kg SC bid | Acute MI | |
| **Epinephrine** | anaphylaxis: 0.3-0.5 mg IM;<br>ACLS cardiac arrest: 1mg IV q3-5 min<br>ACLS bradycardia: 2-10mcg/min IV infusion | Anaphylaxis, ACLS cardiac arrest, ACLS bradycardia | Max 1 mg/dose |
| **Fentanyl** | 0.5-1.0 µg/kg IV | Procedural sedation | Very short acting narcotic (complication=apnea) |
| **Flumazenil** | 0.3 mg IV bolus q5min x 3 doses | Reversal of procedural sedation | Benzodiazepine antagonist<br>Can cause seizures/status epilepticus in chronic benzodiazepine users |
| **Furosemide (Lasix®)** | CHF: 40-80 mg IV<br>HTN: 10-40 mg PO bid | CHF<br>HTN | Monitor for electrolyte imbalances |
| **Glucose** | 0.5-1.0 g/kg (1-2 mL/kg) IV of D50W | Hypoglycemia/DKA | |
| **Haloperidol** | 2.5-5.0 mg PO/IM initial effective dose<br>6-20 mg/d | Psychosis<br>Cannabis Hyperemesis Syndrome | Monitor for side effects if prescribing to a patient with Parkinson's disease (extrapyramidal side effects); results in CNS depression |
| **Ibuprofen** | 200-800 mg PO tid prn max 1200 mg/d | Mild to moderate acute pain<br>Analgesic and anti-inflammatory properties | |
| **Insulin** | bolus 5-10 U (0.2 U/kg)<br>then 5-10 U (0.1 U/kg) per h | Hyperglycemia | Monitor blood glucose levels<br>Consider $K^+$ replacement, also measure blood glucose levels before administration |
| **Ipratropium bromide** | 2-3 puffs inhaled tid-qid, max 12 puffs/d | Asthma | Contraindications include: peanut/soy allergy<br>Caution with narrow-angle glaucoma |
| **Lidocaine with epi** | max 7 mg/kg SC | Local anesthetic | Not to be used in fingers, nose, toes, penis, ears |
| **Lidocaine w/o epi** | max 5 mg/kg SC | Local anesthetic | |
| **Lorazepam** | anxiety: 0.5-2 mg PO/IM/IV q6-8h<br>status epilepticus: 4 mg IV repeat up to q5min | Anxiety<br>Status epilepticus<br>Alcohol withdrawal | |
| **Midazolam** | 50 µg/kg IV | Procedural sedation | Short acting benzodiazepine (complication=apnea when used with narcotic)<br>Fentanyl and midazolam often used together for procedural sedation |

**Table 41. Commonly Used Medications** (continued)

| Drug | Dosing Schedule | Indications | Comments |
|---|---|---|---|
| **Morphine** | 10-30 mg PO q4h<br>2.5-5mg IV q4h | Mild to moderate acute/chronic pain<br>Prescribed in combination with NSAIDs or acetaminophen | GI and constipation side effects<br>DO NOT CRUSH, CUT, or CHEW<br>Risk of tolerance |
| **Naloxone** | 0.5-2 mg or 0.01-0.02 mg/kg initial bolus IV/IM/SL/SC or via ETT (2-2.5x IV dose), increase dose by 2 mg until response/max 10 mg | Comatose patient<br>Opioid overdose<br>Reversal in procedural sedation | If patient is a chronic opioid user begin with very small doses, and go up with small increments as needed |
| **Nitroglycerin** | acute angina: 0.3-0.6 mg SL q5min, OR 5 µg/min IV increasing by 5-20 µg/min q3-5min | Angina<br>Acute MI | Not to be used with other antihypertensives<br>Not in right ventricular MI |
| **Percocet 10/325®** | 1-2 tabs PO q6h prn | Moderate pain control | Oxycodone + acetaminophen<br>Max 4 g acetaminophen daily |
| **Phenytoin** | Status epilepticus: see Table 17 | Status epilepticus | Begin maintenance dose 12 h after loading dose<br>Continuous ECG, BP monitoring mandatory |
| **Polysporin®** | Apply to affected area bid-tid | Superficial infections | |
| **Propofol** | 0.25-1 mg/kg IV | Procedural sedation, also refractory status epilepticus | Short acting<br>Anesthetic/sedative (complication=apnea, decreased BP) |
| **Salbutamol** | 2 puffs inhaled q4-6h max 12 puffs/d | Asthma<br>Reactive airways | Caution with cardiac abnormalities |
| **Thiamine** | 100 mg IV/IM initially, then 50-100 mg IM/IV/PO OD x 3d | To treat/prevent Wernicke's encephalopathy | Caution use in pregnancy |
| **Tylenol #3®** | 1-2 tabs PO q4-6h prn | Pain control | Acetaminophen + Codeine<br>Metabolism of codeine is highly variable<br>Max 4 g acetaminophen daily |

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# Endocrinology

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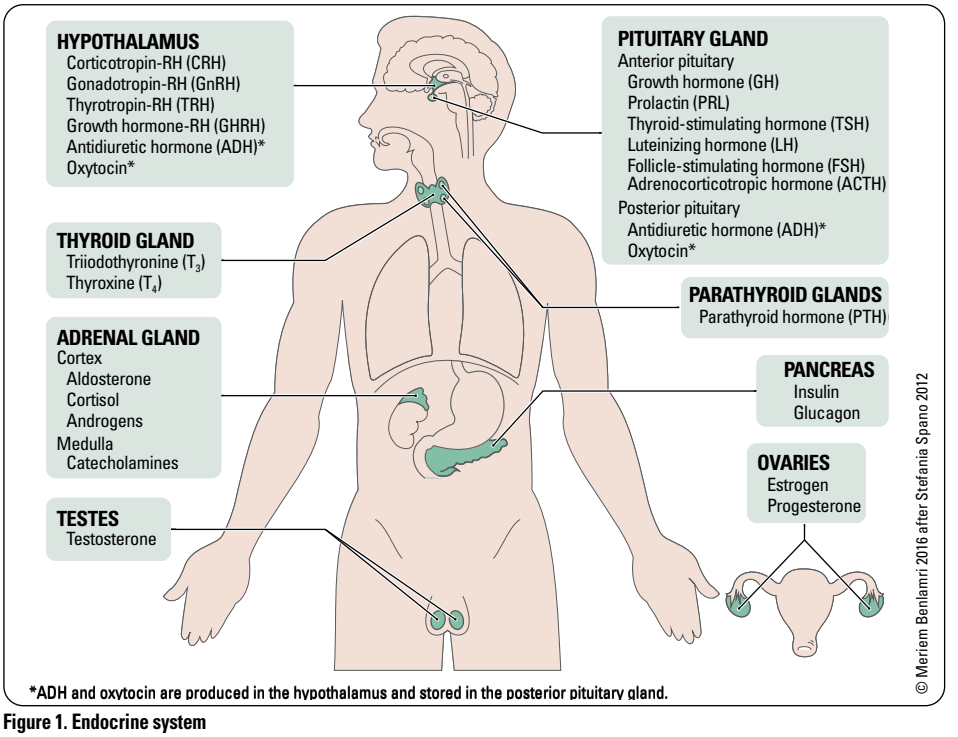
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# Acronyms

| | |
|---|---|
| [ ] | concentration |
| Ab | antibody |
| ACR | albumin-creatinine ratio |
| ACTH | adrenocorticotropic hormone |
| ADH | antidiuretic hormone |
| AG | anion gap |
| AVP | arginine vasopressin |
| BG | blood glucose |
| BMD | bone mineral density |
| BMI | body mass index |
| CAD | coronary artery disease |
| CAH | congenital adrenal hyperplasia |
| CHO | carbohydrates |
| CK | creatine kinase |
| CMV | cytomegalovirus |
| CrCl | creatinine clearance |
| CRH | corticotropin releasing hormone |
| CVD | cardiovascular disease |
| DDAVP | desmopressin (1-deamino-8-D-arginine vasopressin) |
| DHEA | dehydroepiandrosterone |
| DI | diabetes insipidus |
| DKA | diabetic ketoacidosis |
| DM | diabetes mellitus |
| DXM | dexamethasone |
| ECF | extracellular fluid |
| EtOH | ethanol |
| FFA | free fatty acids |
| FNA | fine needle aspiration |
| FPG | fasting plasma glucose |
| FSH | follicle stimulating hormone |
| GFR | glomerular filtration rate |
| GH | growth hormone |
| GHRH | growth hormone releasing hormone |
| GnRH | gonadotropin releasing hormone |
| Hb | hemoglobin |
| hCG | human chorionic gonadotropin |
| HDL | high density lipoprotein |
| HHS | hyperosmolar hyperglycemic state |
| HLA | human leukocyte antigen |
| HMG-CoA | 3-hydroxy-3-methylglutaryl-coenzyme A |
| HPA | hypothalamic pituitary adrenal |
| hs-CRP | highly sensitive C-reactive protein |
| HVA | homovanillic acid |
| ICF | intracellular fluid |
| IDL | intermediate density lipoprotein |
| IFG | impaired fasting glucose |
| IGT | impaired glucose tolerance |
| LCAT | lecithin-cholesterol acyltransferase |
| LDL | low density lipoprotein |
| LH | luteinizing hormone |
| LP | lipoprotein |
| MEN | multiple endocrine neoplasia |
| MMI | methimazole |
| MTC | medullary thyroid cancer |
| NS | normal saline |
| OGTT | oral glucose tolerance test |
| PAD | peripheral arterial disease |
| PCOS | polycystic ovarian syndrome |
| POMC | pro-opiomelanocorticotropin |
| PRL | prolactin |
| PTH | parathyroid hormone |
| PTU | propylthiouracil |
| RAIU | radioactive iodine uptake |
| RAAS | renin-angiotensin-aldosterone system |
| RH | releasing hormone |
| SHBG | sex hormone binding globulin |
| T1DM | Type 1 diabetes mellitus |
| T2DM | Type 2 diabetes mellitus |
| T3 | triiodothyronine |
| T4 | thyroxine |
| TBG | thyroid binding globulin |
| TC | total cholesterol |
| TG | triglycerides |
| TgAb | thyroglobulin antibodies |
| TPOAb | anti-thyroid peroxidase antibodies |
| TRAb | TSH receptor antibodies |
| TRH | thyrotropin releasing hormone |
| TSH | thyroid stimulating hormone |
| TSI | thyroid stimulating immunoglobulin |
| VLDL | very low density lipoprotein |
| VMA | vanillylmandelic acid |
| WC | waist circumference |

# Basic Anatomy Review

## Major Endocrine Organs




*ADH and oxytocin are produced in the hypothalamus and stored in the posterior pituitary gland.

**Figure 1. Endocrine system**



**GENERAL FUNCTION OF ORGANS**

**The Hypothalamic-Pituitary Axis**
External environmental signals (e.g. temperature and light), internal environmental inputs (e.g. glycemia, blood osmolality), and peripheral hormonal feedback are integrated at the coordinating centre of the endocrine system, the hypothalamus. This small region of the brain, which is fundamental to maintaining homeostasis, then sends signals to the pituitary to release hormones that affect the function of the thyroid, adrenals, and gonads as well as influence uterine contraction, lactation, growth, and water balance. On the other hand, the pituitary is regulated by hypothalamic and target organ inputs as well as by its own secretions

**Anatomy ⟷ Function**
Hypothalamic hormones: small peptides, non-binding protein → rapid degradation
High [ ] in pituitary-portal blood system
Low [ ] in peripheral circulation
Proximity of axis preserves the pulsatile output signals from the hypothalamic neurons

**Thyroid**
Thyroid hormone is critical to 1) brain and somatic development in fetus and infants, 2) metabolic activity in adults, and 3) function of virtually every organ system

**Adrenal**
Adrenal glands (6-8g) produce a variety of hormones. Structure, each gland has an outer cortex (3 layers: zona glomerulosa → aldosterone; zona fasciculata → cortisol; zona reticularis → androgen and estrogen precursors) and inner medulla (stores and synthesizes epinephrine and noradrenaline)

**Gonads**
Bifunctional: sex steroid synthesis and gamete production
Sex steroids control sexuality and affect metabolic and brain functions

**Parathyroid**
Synthesize and secrete PTH, a principle regulator of ECF $Ca^{2+}$, regulated by $[Ca^{2+}]$, $[Mg^{2+}]$, $1,25(OH)_2D$ (active metabolite of vitaminD), and phosphate

**Pancreas**
Endocrine islet β-cells produce insulin: oppose glucose production (glycogenolysis, gluconeogenesis), increase glucose uptake into muscle and fat. Glucagon, epinephrine, cortisol, and GH are the counterregulatory hormones

# Dyslipidemias

### Definition
- metabolic disorders characterized by elevations of fasting plasma LDL-cholesterol, and/or triglycerides (TG), and/or low HDL-cholesterol

## Overview of Lipid Transport

- lipoproteins are spherical complexes that consist of a lipid core surrounded by a shell of water-soluble cholesterol, apolipoproteins, and phospholipids
- lipoproteins transport lipids within the body
- apolipoproteins serve as enzyme co-factors, promote clearance of the particle by interacting with cellular receptors, and stabilize the lipoprotein micelle

**Table 1. Lipoproteins**

| Lipoprotein | Function |
|---|---|
| **Chylomicron** | Transports dietary TG from gut to adipose tissue and muscle |
| **VLDL** | Transports hepatic synthesized TG from liver to adipose tissue and muscle |
| **IDL** | Product of hydrolysis of TG in VLDL by lipoprotein lipase resulting in depletion of TG core<br>Enriched in cholesterol esters |
| **LDL** | Cholesterol rich atherogenic particles<br>Formed by further removal of residual TG from IDL core by hepatic lipase |
| **HDL** | Transports cholesterol from peripheral tissues to liver<br>Acts as a reservoir for apolipoproteins |

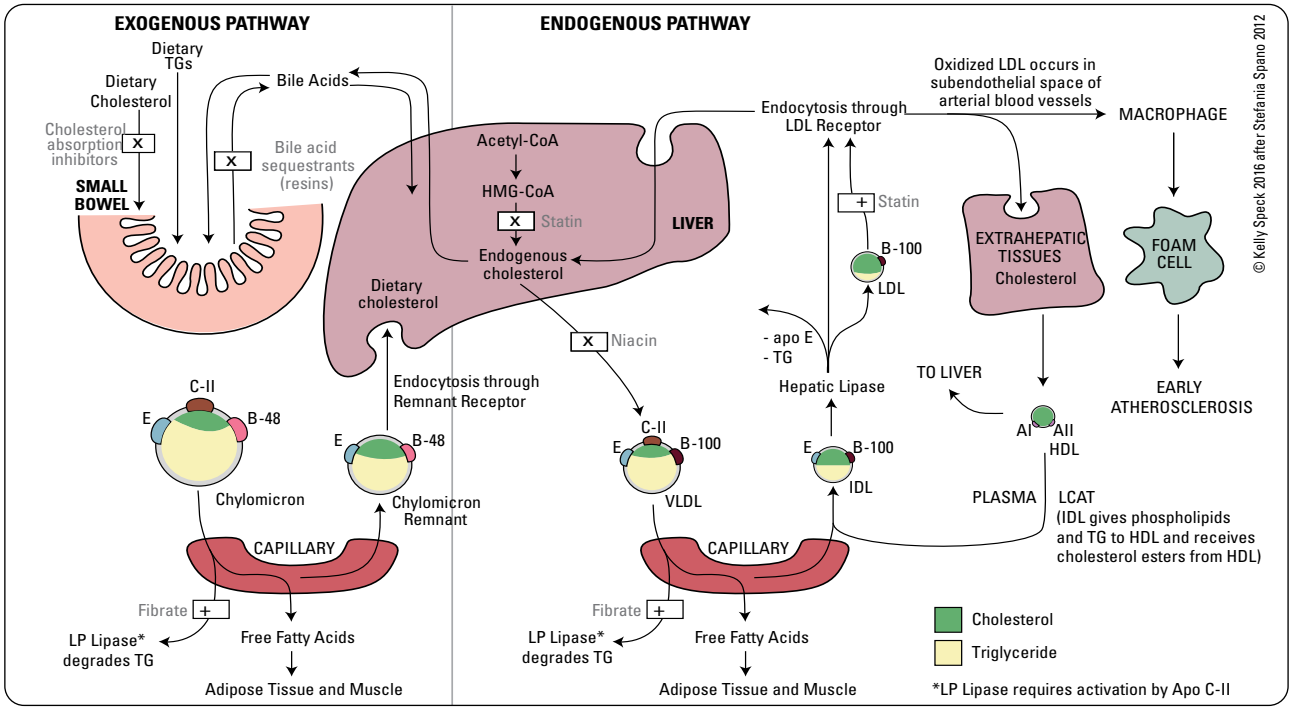



**Figure 2. Exogenous and endogenous biosynthetic lipid pathways**

# Primary Dyslipidemias (rare)

## Definition

- caused by a genetic defect in lipid metabolism

**Table 2. Primary Dyslipidemias**

| Condition | Main Lab Abnormality | Mechanism | Clinical Feature | Treatment |
|---|---|---|---|---|
| **Familial Hypercholesterolemia** | ↑ Total cholesterol<br>↑ LDL cholesterol | Genetic defect in LDLR<br>Can be homozygous or heterozygous inhibiting liver's ability to clear LDL from the circulation | Tendinous xanthomatosis (achilles, patellar, and extensor tendons of hand)<br>Arcus cornealis<br>Xanthelasmata<br>Heterozygotes: premature CAD, 50% risk of MI in men by age 30<br>Homozygotes: manifest CAD and other vascular disease early in childhood and can be fatal (in <20 yr olds) | Maximally tolerated statin as initial drug therapy, addition of second drug (ezitimibe and/or PCSK9 inhibitor) as second line, third line for homozygotes is portacaval shunt or LDL apheresis; potential liver transplant<br>Refer to lipid specialist in drug-resistant hypercholesterolemia |
| **Hereditary Chylomicronemia**<br>**Familial lipoprotein lipase deficiency**<br>**ApoC2 deficiency** | ↑ TG from excess chylomicron particles) | Lipoprotein lipase deficiency: Prevents proper digestion and storage of fats leading to massive accumulation of triglyceride rich chylomicron particles<br>$ApoC_2$ deficiency: prevents activation of lipoprotein lipase leading to massive accumulation of triglyceride rich chylomicron particles | Presents at infancy (LPL), adolescence to adulthood ($APOC_2$)<br>Abdominal complaints (pain, hepatosplenomegaly, pancreatitis)<br>Lipemia retinalis<br>Eruptive xanthomata | <10-15% of calories from fat<br>Supplement with essential fatty acids, fat-soluble vitamins<br>Plasma transfusion may help individuals with $APOC_2$ mutation |
| **Familial Hypoalphalipoproteinemia** | ↓ HDL cholesterol | Autosomal dominant inheritance of a mutation in the ABCA1 or the APOA1 gene | Premature atherosclerosis<br>Cerebrovascular disease | Reduce the risk of atherosclerosis with lifestyle changes, management of concomitant hypercholesterolemia, hypertriglyceridemia, and metabolic syndrome if present |
| **Tangier Disease** | ↓ HDL cholesterol | Autosomal recessive inheritance of mutations in the ABCA1 gene<br>Impaired HDL-mediated cholesterol efflux from macrophages and impaired intracellular lipid trafficking | Mild hypertriglyceridemia<br>Neuropathy<br>Enlarged, orange-coloured tonsils<br>Premature atherosclerosis<br>Splenomegaly<br>Hepatomegaly<br>Corneal clouding<br>T2DM | Reduce the risk of atherosclerosis with lifestyle changes, management of concomitant hypercholesterolemia, hypertriglyceridemia, and metabolic syndrome if present |

# Secondary Dyslipidemias

## Definition

- caused by acquired medical conditions or lifestyle factors that affect lipid metabolism

**Table 3. Etiology Secondary Dyslipidemias**

| Hypercholesterolemia | Low HDL | Hypertriglyceridemia |
|---|---|---|
| Endocrine: hypothyroidism (small dense LDL with T2DM and obesity, with normal LDL level)<br><br>Renal: nephrotic syndrome<br><br>Immunologic: monoclonal gammopathy<br><br>Hepatic: cholestatic liver disease (e.g. primary biliary cirrhosis)<br><br>Nutritional: anorexia nervosa<br><br>Drugs: cyclosporin, carbamazepine | Endocrine: obesity/metabolic syndrome, DM<br><br>Drugs: β-blockers, anabolic steroids<br><br>Other: acute infections, inflammatory conditions | Endocrine: Obesity/metabolic syndrome Diabetes<br><br>Lifestyle: Alcohol, high carbohydrate/ high fat diet<br><br>Drugs: corticosteroids, estrogen, hydrochlorothiazide, retinoic acid, β-blockers without intrinsic sympathomimetic action (ISA), anti-retroviral drugs, atypical antipsychotics, oral contraceptive pills<br><br>Other: pregnancy |

# Dyslipidemia and the Risk for Coronary Artery Disease

- increased LDL is a major risk factor for atherosclerosis and CAD as LDL is the major atherogenic lipid particle
- increased HDL is associated with decreased cardiovascular disease and mortality
- moderate hypertriglyceridemia (triglyceride level 2.3-9 mmol/L) is an independent risk factor for CAD, especially in people with DM and in post-menopausal women
- treatment of hypertriglyceridemia has not been shown to reduce CAD risk

## Screening

- screen men and women >40 yr or post-menopausal
- if following risk factors present, screen at any age:
  - DM
  - current cigarette smoking or COPD
  - HTN (sBP >140, dBP >90), hypertensive diseases of pregnancy
  - obesity (BMI 30 kg/m$^2$)
  - family history of premature CVD
  - clinical signs of hyperlipidemia (xanthelasma, xanthoma, arcus cornealis)
  - clinical evidence of abdominal aneurysm
  - clinical evidence of atherosclerosis
  - inflammatory disease (rheumatoid arthritis, SLE, psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease)
  - HIV infection on highly active anti-retroviral therapy (HAART)
  - chronic kidney disease (estimated GFR <60 mL/min/1.73 m$^2$)
  - erectile dysfunction
  - high risk ethnicity: south Asian, First Nations
- screen children with a family history of hypercholesterolemia or chylomicronemia
- apolipoprotein B (apo B)
  - each atherogenic particle (VLDL, IDL, LDL, and lipoprotein A) contains one molecule of apo B
  - serum [apo B] reflects the total number of particles and may be useful in assessing cardiovascular risk and adequacy of treatment in high risk patients and those with metabolic syndrome
- Lipoprotein A, (Lp(a)), levels may help stratifying those at intermediate risk
- coronary artery calcium (CAC) may help stratifying those at intermediate risk
- C-reactive protein (hs-CRP) levels
  - highly sensitive acute phase reactant
  - may be clinically useful in identifying those at a higher risk of cardiovascular disease than predicted by the global risk assessment

## CVD Risk Assessment

- Framingham Risk Score (FRS): 10 yr risk of major CVD event. Calculated based on gender, age, total cholesterol, HDL, sBP, and smoking (>20%: high risk; 10-19%: moderate risk; <10% low risk)
- Reynolds Risk Score: 10 yr risk of major CVD event. Calculated based on age, SBP, total cholesterol, HDL, high sensitivity CRP, family history of MI



**Familial Hypercholesterolemia and Cardiovascular Risk Calculators**

- Risk calculators such as Framingham and SCORE do not apply to patients with familial hypercholesterolemia
- Consider all adults with FH as "high risk"



**Treatment Effect**

Each 1.0 mmol/L decrease in LDL corresponds to 20-25% relative risk reduction in cardiovascular disease



**6% Rule**

If the dose of a statin is doubled, there is approximately a 6% increase in the LDL lowering efficacy



**For Statin Follow-Up**

- Liver enzymes and lipid profile: liver enzymes measured at the beginning of treatment then once after therapy initiated. Lipids (once stabilized) measured annually. Order both if patient complains of jaundice, RUQ pain, dark urine
- CK at baseline and if patient complains of myalgia
- D/C statin if CK >10x upper limit of normal or patient has persistent myalgia



**The American Approach to LDL Lowering A Report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines**

Circulation 2013;00:000-000

**Purpose**: To examine the evidence supporting specific end-point LDL targets in statin therapy.

**Study**: Systematic review, searching 1995-2009 inclusive identified 19 RCTs.

**Results**: None of the trials examined demonstrated better cardiovascular outcomes for a particular target LDL. Moreover, many trials showed best outcomes from maximum tolerated dose of statin, irrespective of the treated LDL level.

**Conclusion**: Based on systematic review, the ACC/AHA is no longer recommending a "Treat to Target" approach for statin therapy. Primary prevention in patients with increased risk should be treated with moderate to high intensity statin therapy without tracking LDL targets. Similarly, patients needing secondary prevention should receive high intensity statin therapy without attention to LDL targets.

# Treatment of Dyslipidemias

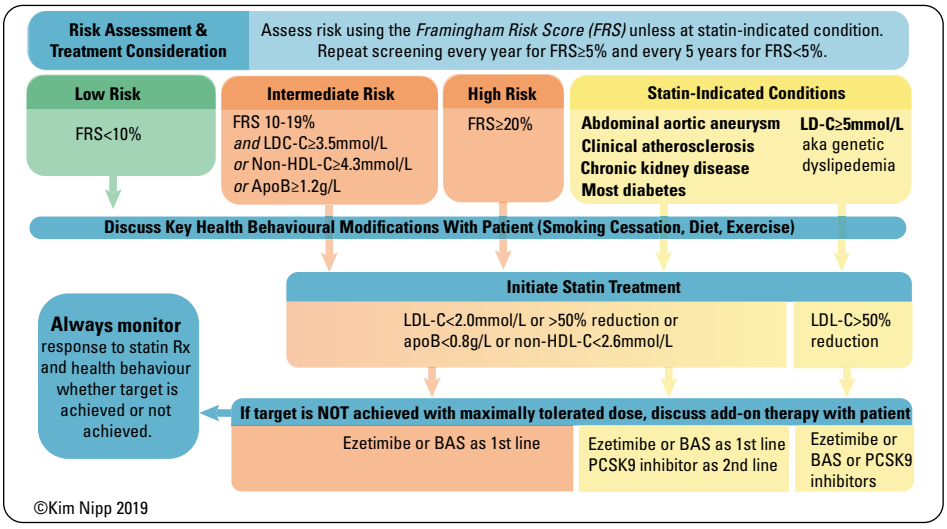



**Figure 3. Dyslipidemia management for the prevention of cardiovascular disease in the adult**
Adapted from 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Canadian Cardiovascular Society.

## Approach to Treatment

For clinical guidelines see Can J Cardiol 2016;32:1263-1282

- consider treatment for patients with statin-indicated conditions (e.g. Type II DM); risk assessment is not required
- risk stratification and treatment: The primary target of therapy is to achieve an LDL <2.0 mmol/L or a 50% reduction in LDL from baseline

**Table 4. Treatment of Dyslipidemia**

| Category | Consider initiating pharmacotherapy if: | Target |
|---|---|---|
| **Primary Prevention** | High Risk (FRS ≥20%)<br>Intermediate Risk<br>((FRS 10-19% and LDL-C ≥ 3.5 mmol/L)<br>Or non-HDL-C ≥ 4.3 mmol/L or ApoB ≥ 1.2 g/L or<br>Men ≥ 50 and women ≥ 60 with one additional risk factor: low HDL-c, impaired fasting glucose, high waist circumference, smoker, HTN) | LDL-C <2.0 mmol/L<br>Or<br>50% reduction from baseline |
| **Statin-Indicated Conditions** | Clinical atherosclerosis (MI, ACS, stroke, TIA, carotid disease, peripheral artery disease)<br>Abdominal aortic aneurysm (>3 cm) or previous aneurysm surgery<br>DM ≥40 yr<br>15 yr duration for age ≥30 yr (T1DM)<br>Microvascular disease<br>Chronic kidney disease (age ≥50 yr)<br>eGFR <60 mL/min/1.73m$^2$ or<br>ACR >3 mg/mmol<br>LDL-C ≥5.0 mmol/L | LDL-C <2.0 mmol/L<br>Or<br>50% reduction from baseline |

# Disorders of Glucose Metabolism

## Overview of Glucose Regulation

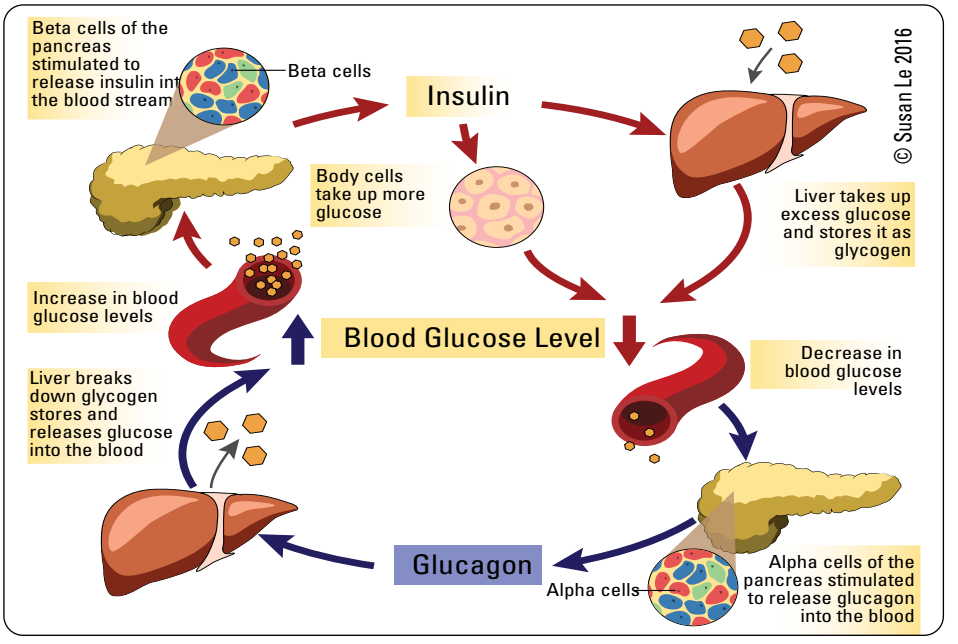



**Figure 4. Blood glucose regulation**

## Pre-Diabetes (Impaired Glucose Tolerance/ Impaired Fasting Glucose)

- 1-5% per yr go on to develop DM
- 50-80% revert to normal glucose tolerance
- weight loss may improve glucose tolerance (5-10% of body weight)
- increased risk of developing macrovascular complications (IGT >IFG)
- lifestyle modifications decrease progression to DM by 58%

### Diagnostic Criteria (CDA Guidelines)

- impaired fasting glucose (IFG): fasting plasma glucose (FPG) 6.1-6.9 mmol/L
- impaired glucose tolerance (IGT): 2h 75 g oral glucose tolerance test (OGTT) 7.8-11.0 mmol/L
- HbA1c: 6.0-6.4%

## Diabetes Mellitus

### Definition

- diabetes mellitus is a heterogeneous metabolic disorder characterized by the presence of hyperglycemia due to impairment of insulin secretion, defective insulin action, or both
- chronic hyperglycemia of diabetes is associated with relatively specific long-term microvascular complications affecting the eyes, kidneys and nerves, as well as an increased risk for macrovascular complications such as cardiovascular, stroke, and peripheral vascular disease

**Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein (Jupiter Study)**
NEJM 2008;359(21):2195-207
**Study**: Randomized Control Trial
**Intervention**: Statin Therapy
**Results**: Rosuvastatin reduced LDL cholesterol levels by 50% and high-sensitivity C-reactive protein levels by 37%. The rates of the primary end point were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for rosuvastatin, 0.56; 95% confidence interval [CI], 0.46-0.69; P<0.00001), with corresponding rates of 0.17 and 0.37 for myocardial infarction (hazard ratio, 0.46; 95% CI, 0.30-0.70; P=0.0002), 0.18 and 0.34 for stroke (hazard ratio, 0.52; 95% CI, 0.34-0.79; P=0.002), 0.41 and 0.77 for revascularization or unstable angina (hazard ratio, 0.53; 95% CI, 0.40-0.70; P<0.00001), 0.45 and 0.85 for the combined end point of myocardial infarction, stroke, or death from cardiovascular causes (hazard ratio, 0.53; 95% CI, 0.40-0.69; P<0.00001), and 1.00 and 1.25 for death from any cause (hazard ratio, 0.80; 95% CI, 0.67-0.97; P=0.02)
**Conclusion**: Statins reduce the incidence of major cardiovascular events even in healthy people without hyperlipidemia but with elevated C-reactive protein.

**Three Year Efficacy of Complex Insulin Regimens in T2DM: 4T Trial**
NEJM 2009;361:1736-1747
**Study**: Randomized unblinded trial with 3 yr of follow-up.
**Population**: 708 patients with T2DM, not on insulin or thiazolidinedione therapy on maximal metformin and sulfonylurea therapy.
Intervention: Thrice-daily prandial insulin aspart, versus twice-daily biphasic insulin aspart, versus once-daily basal insulin detemir. Sulfonylurea therapy was replaced with a secondary insulin regime specific to each arm if there was persistent hyperglycemia.
**Primary Outcome:** Three yr hemoglobin HbA1c.
**Results**: Significant difference in rates of patient withdrawal from the study: 5.1% biphasic, 11.7% prandial, 8.5% basal regimens (p=0.04). There were no significant differences in median HbA1c levels between all three arms from yr 1-3. A smaller proportion of patients reached HbA1c <6.5% or <7.0% in the biphasic arm. The basal arm had least weight gain and least weight circumference increase, but highest rate of secondary insulin requirement. The basal arm had fewest severe hypoglycemic events per patient year, while the biphasic had the most serious adverse effects.
**Conclusion**: Basal insulin regime provides the best glycemic control over a 3 yr study, with better HbA1c control, fewer hypoglycemic events, and less weight gain.

## Diagnostic Criteria (as per Diabetes Canada 2018 Clinical Practice Guidelines)

- any one of the following is diagnostic:

### Table 5. Diagnosis of Diabetes

**FPG ≥7.0 mmol/L**
Fasting = no caloric intake for at least 8 hours

or

**HbA1C ≥6.5% (in adults)**
Not for diagnosis of suspected T1DM, children, adolescents, or pregnant women

or

**2hPG in a 75g OGTT ≥11.1mmol/L**

or

**Random PG ≥11.1 mmol/L**
Random = any time of the day, without regard to the interval since last meal

- in the presence of hyperglycemia symptoms (polyuria, polydipsia, polyphagia, weight loss, blurry vision), a confirmatory test is not required
- in the absence of hyperglycemic symptoms, a repeat confirmatory test (FPG, A1C, 2hPG in a 75 g OGTT) done on another day is required for diagnosis of diabetes

## Etiology and Pathophysiology

### Table 6. Etiologic Classification of Diabetes Mellitus

**I. T1DM** (immune-mediated β cell destruction, usually leading to absolute insulin deficiency)

**II. T2DM** (Type 2 diabetes occurs when the pancreas does not produce enough insulin or when the body does not effectively use the insulin that is produced)

**III. Other Specific Causes of DM**

a. Genetic defects of β cell function (e.g. MODY – Maturity-Onset Diabetes of the Young (also known as monogenic diabetes) or insulin action
b. Diseases of the exocrine pancreas:
Pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis ("bronze diabetes")
c. Endocrinopathies:
Acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism
d. Drug-induced:
Glucocorticoids, thyroid hormone, β-adrenergic agonists, thiazides, phenytoin, antipsychotics
e. Infections:
Congenital rubella, CMV, coxsackie
f. Genetic syndromes associated with DM:
Down's syndrome, Klinefelter's syndrome, Turner's syndrome

**IV. Gestational Diabetes Mellitus** (see Obstetrics, OB26)

### Table 7. Comparison of Type 1 and Type 2 Diabetes Mellitus

| | Type 1 | Type 2 |
|---|---|---|
| **Onset** | Usually <30 yr of age | Usually >40 yr of age<br>Increasing incidence in pediatric population 2º to obesity |
| **Epidemiology** | Traditionally more common in European populations<br>Less common in Asians, Hispanics, Aboriginals, and Blacks<br>Accounts for 5-10% of all DM | More common in Blacks, Hispanics, Aboriginals, and Asians<br>Accounts for >90% of all DM |
| **Etiology** | Autoimmune | Complex and multifactorial |
| **Genetics** | Monozygotic twin concordance is 30-40%<br>Associated with HLA class II DR3 and DR4, with either allele present in up to 95% of T1DM<br>Certain DQ alleles also confer a risk | Greater heritability than T1DM<br>Monozygotic twin concordance is 70-90%<br>Polygenic<br>Non-HLA associated |

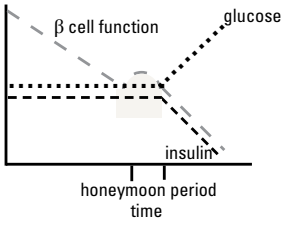
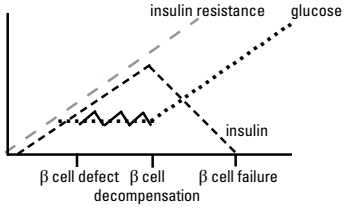
**Effects of Intensive Treatment of T1DM on the Development and Progression of Long-Term Complications: The DCCT Study**
NEJM 1993;329:977-986
**Study:** Multicentre RCT, with 6.5 yr of mean follow-up
**Patients:** 1441 patients (aged 13-39 yr) with T1DM with no cardiovascular history or severe diabetic complications
**Intervention:** Intensive therapy (3 or more daily insulin injections or treatment with an insulin pump with dose adjustments as needed, BG monitoring minimum qid, monthly visits, strict BG targets) vs. conventional therapy (1 or 2 insulin injections per day with no dose adjustments, daily BG monitoring, visits q3mo).
**Outcomes:** Primary outcome was development or progression of retinopathy. Secondary outcomes were development or progression of renal, neurological, cardiovascular, and neuropsychological outcomes.
**Results:** Intensive treatment of T1DM significantly reduced the risk for the development and progression of retinopathy in the primary- and secondary-intervention cohorts, respectively. Intensive therapy also reduced the occurrence of microalbuminuria, albuminuria, and clinical neuropathy. The chief adverse event associated with intensive therapy was an increase in the occurrence of severe hypoglycemia.
**Conclusions:** Intensive treatment of T1DM significantly reduces the development and progression of diabetic retinopathy, nephropathy, and neuropathy in patients with T1DM.

**Blood Glucose Control in T2DM – UKPDS 33**
Lancet 1998;352:837-853
**Study:** RCT (mean follow-up 10 yr).
**Patients:** 3867 patients with newly diagnosed T2DM (mean age 53 yr, 61% men, 81% white, mean fasting plasma glucose [FPG] 6.1-15.0 mmol/L). Exclusions included severe cardiovascular disease, renal disease, retinopathy, and others.
Intervention: Intensive treatment with a sulfonylurea or insulin (target FPG <6 mmol/L) vs. conventional treatment with diet alone (target FPG <15 mmol/L without hyperglycemic symptoms).
**Main Outcomes:** DM-related endpoints (MI, angina, heart failure, stroke, renal failure, amputation, retinopathy, blindness, death from hyperglycemia or hypoglycemia), DM-related death, and all-cause mortality.
**Results:** Patients allocated to intensive treatment had lower median HbA1c levels (p<0.001).

| Outcome | RRR % (p value) |
|---|---|
| DM-related endpoint | 12 (0.029) |
| DM-related death | 10 (0.34) |
| All-cause mortality | 6 (0.44) |

Patients allocated to intensive therapy had more hypoglycemic episodes and greater weight gain.
**Conclusion:** Intensive blood glucose control reduces microvascular, but not macrovascular complications in T2DM.

**Table 7. Comparison of Type 1 and Type 2 Diabetes Mellitus** (continued)

| | Type 1 | Type 2 |
|---|---|---|
| **Pathophysiology** | Synergistic effects of genetic, immune, and environmental factors that cause β cell destruction resulting in impaired insulin secretion<br>Autoimmune process is believed to be triggered by environmental factors (e.g. viruses, bovine milk protein, urea compounds)<br>Pancreatic cells are infiltrated with lymphocytes resulting in islet cell destruction<br>80% of β cell mass is destroyed before features of DM present | Impaired insulin secretion, peripheral insulin resistance (likely due to receptor and post-receptor abnormality), and excess hepatic glucose production |
| **Natural History** |  <br>After initial presentation, honeymoon period often occurs where glycemic control can be achieved with little or no insulin treatment as residual cells are still able to produce insulin<br>Once these cells are destroyed, there is complete insulin deficiency |  <br>Early on, glucose tolerance remains normal despite insulin resistance as β cells compensate with increased insulin production<br>As insulin resistance and compensatory hyperinsulinemia continue, the β cells are unable to maintain the hyperinsulinemic state which results in glucose intolerance and DM |
| **Circulating Autoantibodies** | Islet cell Ab present in up to 60-85%<br>Most common islet cell Ab is against glutamic acid decarboxylase (GAD)<br>Up to 60% have Ab against insulin | <10% |
| **Risk Factors** | Personal history of other autoimmune diseases including Graves' disease, myasthenia gravis, autoimmune thyroid disease, celiac disease, and pernicious anemia<br>Family history of autoimmune diseases | Age >40 yr<br>Schizophrenia<br>Abdominal obesity/overweight<br>Fatty liver<br>First-degree relative with DM<br>Hyperuricemia<br>Race/ethnicity (Black, Aboriginal, Hispanic, Asian-American, Pacific Islander)<br>Hx of IGT or IFG<br>HTN<br>Dyslipidemia<br>Medications e.g. 2nd generation antipsychotics<br>PCOS<br>Hx of gestational DM or macrosomic baby (>9 lb or >4 kg) |
| **Body Habitus** | Normal to thin | Typically overweight with increased central obesity |
| **Treatment** | Insulin | Lifestyle modification<br>Non-insulin antihyperglycemic agents - unless contraindicated, metformin should be the initial antihyperglycemic agent of choice. Additional agents to be selected on the basis of clinically relevant issues, such as glucose-lowering effectiveness, risk of hypoglycemia, and effect on body weight<br>Insulin therapy |
| **Acute Complication** | Diabetic ketoacidosis (DKA) in severe cases | Hyperosmolar hyperglycemic state (HHS)<br>DKA in severe cases |
| **Screening** | Subclinical prodrome can be detected in first and second-degree relatives of those with T1DM by the presence of pancreatic islet autoantibodies | Screen individuals with risk factors |

**Diabetes Canada 2018 Clinical Practice Guidelines**

| | Target |
|---|---|
| HbA1c | <7.0% (most adults) |
| Fasting plasma glucose | 4-7 mmol/L (72-126 mg/dL) |
| 2h post-prandial glucose | 5-10 mmol/L (90-180 mg/dL)<br>5-8 mmol/L (90-144 mg/dL) if not meeting target A1c and can be safely achieved |
| Lipids | As per high risk group if age >40 or age >30 if DM duration >15 yr |
| Blood pressure | <130/80 |

# Treatment of Diabetes

## Glycemic Targets

- HbA1c reflects glycemic control over 3 mo and is a measure of patient's long-term glycemic control
- therapy in most individuals with T1DM or T2DM (especially younger patients) should be targeted to achieve a HbA1c ≤7.0% in order to reduce the risk of microvascular and if implemented early in the course of disease, macrovascular complications
- more intensive glucose control, HbA1c <6.5%, may be targeted in patients with a shorter duration of DM with no evidence of significant CVD and longer life expectancy, to further reduce risk of nephropathy and retinopathy, provided this does not result in a significant increase in hypoglycemia
- less stringent HbA1c targets (7.1-8.5%) may be more appropriate in patients with limited life expectancy, higher level of functional dependency, a history of recurrent severe hypoglycemia, multiple comorbidities, extensive CAD, or a failure to acheive an HbA1c <7.0% despite intensified basal and bolus insulin therapy
- there may be harm associated with strategy to target HbA1c <6.0% (see sidebar ACCORD Trial, E9)

**ABCDES of Diabetes Care**
**A**1c targets (<7.0%)
**B**lood pressure (<130/80)
**C**holesterol (LDL-C <2.0 mmol/L)
**D**rugs for CVD risk reduction
**E**xercise goals and healthy eating
**S**moking cessation and screening for complications

## Diet
- daily carbohydrate intake 45-60% of energy, protein 15-20% of energy, and fat <35% of energy
- intake of saturated fats <7% and polyunsaturated fats <10% of total calories each
- limit sodium, alcohol, and caffeine intake
- Type 1: carbohydrate counting is used to titrate prandial insulin dose
- Type 2: weight reduction to help control blood glucose levels

## Lifestyle
- regular physical exercise to improve insulin sensitivity, lower lipid concentrations, and control blood pressure. At least 150 minutes per week of aerobic exercise and at least 2 sessions per week of resistance exercise are recommended
- smoking cessation

## Medical Treatment: Non-Insulin Antihyperglycemic Agents (T2DM)
- initiate non-insulin antihyperglycemic therapy within 2-3 mo if lifestyle management does not result in glycemic control
- if initial HbA1c >8.5% at the time of diagnosis, initiate pharmacologic therapy with metformin immediately, and consider combination of therapies or insulin immediately
- continue to add additional pharmacologic therapy in a timely fashion to achieve target HbA1C within 3-6 mo of diagnosis
- see *Common Medications*, E52 for details on antihyperglycemic agents

## Medical Treatment: Insulin
- used for T1DM at onset, may be used in T2DM at any point in treatment
- routes of administration: subcutaneous injections, continuous subcutaneous insulin infusion pump, IV infusion (regular insulin only)
- basal insulin: control blood sugar (produced by liver) during periods of fasting; slow onset of action, lasts a long time
- bolus insulin: required to dispose of glucose from a meal; rapid onset of action, short acting
- bolus insulins: short-acting (Insulin regular), rapid-acting analogue (Insulin aspart, Insulin glulisine, Insulin lispro)
- basal insulins: intermediate-acting (Insulin NPH), long-acting analogue (Insulin detemir, glargine, degludec)
- premixed insulins (combination of basal and bolus insulins), 30/70 insulin mixture, Humalog® mix 25, Novorapid® mix 30
- estimated total daily insulin requirement: often start with 0.3-0.5 units/kg/d

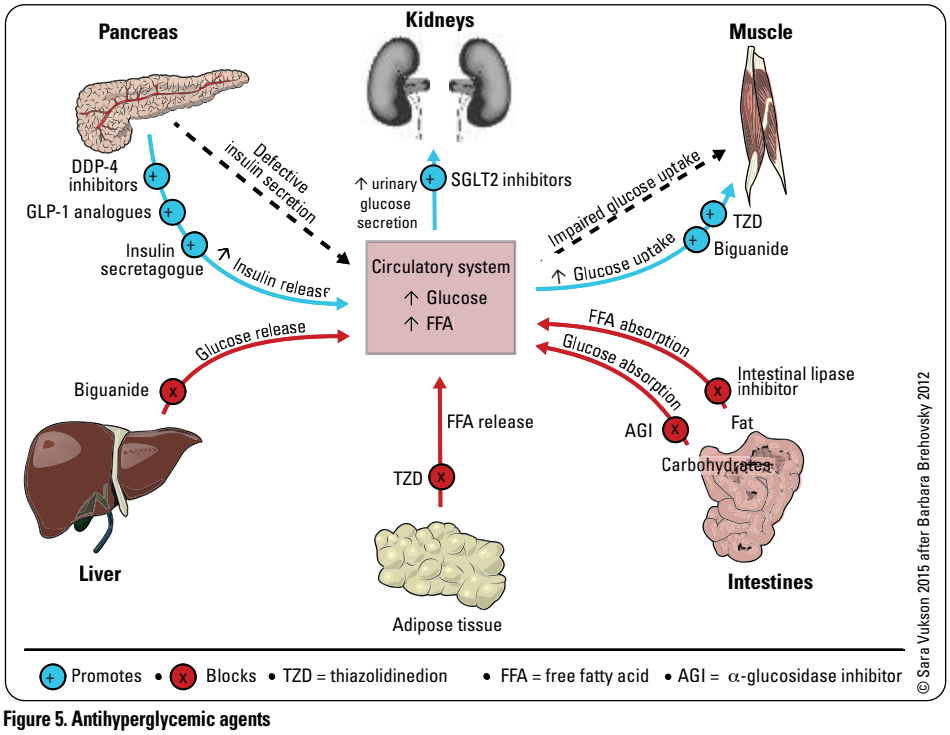



**Figure 5. Antihyperglycemic agents**

**Effects of Intensive Glucose Lowering in T2DM: The ACCORD Trial**
NEJM 2008;358:2545-2559
**Study**: Multicentre RCT.
**Patients**: 10,251 patients (mean age 62.2) with T2DM, and cardiovascular risk factors.
**Intervention**: Intensive therapy targeting a HbA1c level of <6.0% or standard therapy targeting 7.0-7.9%.
**Outcomes**: First occurrence of nonfatal MI, nonfatal stroke, or death from CV causes.
**Results**: The intensive therapy arm was stopped early (3.5 yr vs. 5.6 yr planned) due to evidence of increased mortality. There was no difference in primary outcome for either study arm. There was a significant increase in all-cause mortality, CV mortality, nonfatal MI, and CHF in the intensive therapy group. There were increased rates of all hypoglycemic events, any nonhypoglycemic serious adverse events, fluid retention, and weight gain >10 kg, but lower systolic and diastolic blood pressure in the intensive therapy group. There was an increased incidence of elevated ALT (>3x upper limit) and ACE drug use in the standard therapy group.
**Conclusions**: Intensive glucose lowering therapy in T2DM does not improve clinic outcomes and actually increases the risk of mortality with more adverse events compared to standard therapy. Additional research is required to discern the cause.

**Effects of Intensive Blood Pressure Control in T2DM: The ACCORD Trial**
NEJM 2010;362:1575-1585
**Study**: RCT, unblinded with 4.7 yr of mean follow-up.
**Population**: 4733 patients with T2DM, risk factors for cardiovascular (CV) disease, systolic blood pressure (sBP) between 130-180 mmHg.
**Intervention**: sBP control less than 120 mmHg (intensive) or 140 mmHg (standard).
**Primary Outcomes**: Major CV event (composite nonfatal MI, nonfatal stroke, or CV-related death).
**Results**: Mean number of medications at 1 yr for intensive therapy was 3.4 (95% CI 3.4-3.5) versus 2.1 (95% CI 2.1-2.2) for standard therapy. There was a significant increase in all serious adverse events in the intensive treatment arm (3.3% vs. 1.27%, p=<0.001); especially bradycardia or arrhythmia (0.5% vs. 0.13%, p=0.02) and hyperkalemia (0.4% vs. 0.04%, p=0.01). There was no significant difference in primary outcomes in the two study arms, or all-cause mortality. There was a significant reduction in any stroke (0.32%/yr vs. 0.53%/yr, p=0.01) and nonfatal stroke incidences (0.30%/yr vs. 0.47%/yr, p=0.03) in the intensive therapy arm.
**Conclusions**: Intensive BP lowering to less than 120 mmHg vs. 140 mmHg in patients with T2DM and CV risk factors does not reduce major CV event risk reduction except for stroke events.

### Table 8. Available Insulin Formulations

| Insulin Type (trade name) | Onset | Peak | Duration |
|---|---|---|---|
| **PRANDIAL (BOLUS) INSULINS** | | | |
| Rapid-acting insulin analogues | | | |
| Insulin aspart (NovoRapid®) | 10-15 min | 1-1.5 h | 3-5 h |
| Insulin faster aspart (Fiasp®) | 4 min | 1 h | 3-4 h |
| Insulin lispro (Humalog®, Humalog 200 units/mL) | 10-15 min | 1-2 h | 3.5-4.75 h |
| Insulin glulisine (Apidra®) | 10-15 min | 1-1.5 h | 3-5 h |
| Short-acting insulins | | | |
| Humulin R®<br>Novolin Toronto® | 30 min | 2-3 h | 6.5 h |
| **BASAL INSULINS** | | | |
| Intermediate-acting | | | |
| Humulin N®<br>Novolin NPH® | 1-3 h | 5-8 h | Up to 18 h |
| Long-acting basal insulin analogues | | Not applicable | |
| Insulin detemir (Levemir®) | 90 min | | Up to 24 h (detemir 16-24 h) |
| Insulin glargine 100 units/mL (Lantus®/ Basaglar®) | 90 min | | Up to 24 h (glargine 24 h) |
| Insulin glargine 300 units/mL (Toujeo®) | Up to 6 h | | Up to 30 h |
| Insulin glargine (Basaglar®) | 90 min | | Up to 24 h (glargine 24 h) |
| Insulin degludec (Tresiba®) | 60 min | | Ultralong acting (42 h) |
| **PRE-MIXED INSULINS** | | | |
| Premixed regular insulin – NPH<br>Humulin 30/70®<br>Novolin 30/70® | A single vial or cartridge contains a fixed ratio of insulin (% of rapid acting or short-acting insulin to % of intermediate-acting insulin) | | |
| Premixed insulin analogues<br>Biphasic insulin aspart (NovoMix 30®)<br>Insulin lispro/lispro protamine (Humulin 30/70, Novolin 30/70, Novomix 30 and Humalog Mix 25) | | | |

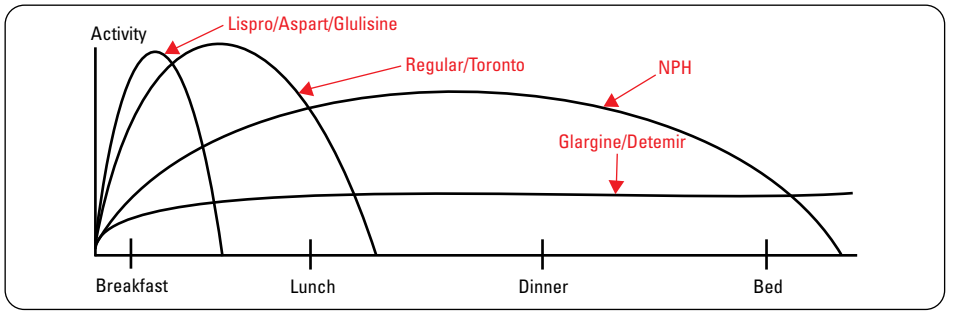



**Figure 6. Duration of activity of different insulins**

## Insulin Regimens

### Table 9. Insulin Regimens for Type 2 DM and Type 1 DM

| | Regimen | Administration |
|---|---|---|
| **T2DM** | Non-insulin antihyperglycemic agent + basal insulin | Start with 10 units of basal insulin at bedtime<br>Titrate up by 1 unit until FPG <7.0 mmol/L |
| **T1DM** | Basal-bolus (multiple daily injections [MDI]) | Estimated total insulin requirement is 0.5-0.7 U/kg<br>40% is given as basal insulin at bedtime<br>20% is given as bolus insulin before breakfast, lunch, and dinner |
| | Premixed | Estimated total insulin requirement is 0.5-0.7 U/kg<br>2/3 dose is given as pre-mixed insulin before breakfast<br>1/3 dose is given as pre-mixed insulin before dinner |

*Bolus insulin: Aspart, Glulisine, Lispro; *Basal insulin: Gargine, Detemir, NPH; *Pre-mixed insulin: Humulin 30/70, Novolin 30/70, Novomix 30, and Humalog Mix2

### Table 10. Titrating Insulin Doses

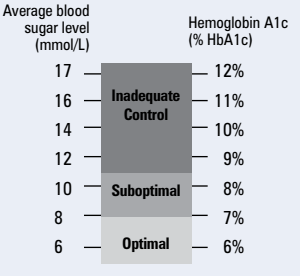
| Hyperglycemic Reading | Insulin Correction |
|---|---|
| High AM sugar | Increase bedtime basal insulin |
| High lunch sugar | Increase AM rapid/regular insulin |
| High supper sugar | Increase lunch rapid/regular insulin, or increase AM basal insulin |
| High bedtime sugar | Increase supper rapid/regular insulin |

**Effects of Combination Lipid Therapy in T2DM: the ACCORD Trial**
NEJM 2010;362:1563-1574
**Study**: RCT, double-blinded trial with 4.7 yr of mean follow-up.
**Population**: 5518 patients with T2DM.
**Intervention**: Statin with or without fibrate therapy.
**Primary Outcome**: Major cardiovascular (CV) event (composite nonfatal MI, nonfatal stroke, or CV-related death).
**Results**: No significant differences in primary outcome between the two arms. No difference in all MI, all stroke, or all-cause mortality between study arms.
**Conclusions**: The addition of fibrate therapy to statin therapy in patients with T2DM does not reduce major CV event risk.

**Effects of a Mediterranean Diet in Preventing Cardiovascular Events in T2DM: The PREDIMED Trial**
NEJM 2013;368:1279-1290
**Study**: RCT, with 4.8 yr of median follow-up.
**Population**: 7447 patients with T2DM or other high cardiovascular risk factors.
**Intervention**: Mediterranean diet supplemented with extra-virgin olive oil, Mediterranean diet supplemented with mixed nuts, or control diet with advice to reduce dietary fat.
**Primary Outcome**: Major cardiovascular (CV) event (MI, stroke, or death from CV causes).
**Results**: Both Mediterranean diets were associated with a reduced incidence of major CV events compared to the control diet.
**Conclusions**: A Mediterranean diet with extra-virgin olive oil or nuts reduces rates of MI, stroke, and CV death in those at high risk for CV disease.

**Sick Day Management**
If patient is ill and is unable to maintain adequate fluid intake, or has an acute decline in renal function, they should hold the following medications:
**SAD MANS** – Sulfonylureuas, ACEIs. Diuretics and direct renin inhibitors, Metformin, ARBs, NSAIDs, SGLT2i

**Conversion Chart for Percentage HbA1c to Average Blood Sugar Control**




Conversion chart adapted from Nathan DM, et al. The clinical information value of a glycosylated hemoglobin assay. *NEJM* 1984;310:341-346

**The 8 Is Precipitating DKA**
**I**nfection
**I**schemia or **I**nfarction
**I**atrogenic (glucocorticoids)
**I**ntoxication
**I**nsulin missed
**I**nitial presentation
**I**ntra-abdominal process (e.g. pancreatitis, cholecystitis)
**I**ntraoperative/perioperative stress

## Insulin Dose Schedules

**Table 11. Insulin Titration and Titration Suggestions for Type 2 DM ' (as per Diabetes Canada 2018 Clinical Practice Guidelines)**

| **Basal Insulin Only – Add-on to Anti-hyperglycemic Agents** | |
|---|---|
| See above summary for A1C, BG targets<br>Most patients will need 40-50 units/d to achieve target but there is no maximum dose<br>Start at a low dose of 10U at bedtime (lower for lean patients <50 kg)<br>Titrate dose accordingly until fasting BG target is achieved (see CDA guidelines for appropriate titration)<br>If fasting hypoglycemia, dose of bedtime basal should be reduced<br>If daytime hypoglycemia, reduce dose of oral anti-hyperglycemic agents (especially secretagogues) | Dosing and Titration Example<br>Starting dose – 10 U at bedtime<br>Increase dose by 1 U every 1 night until fasting BG has reached target of 4-7 mmol/L |
| **Basal-Bolus Insulins** | |
| When addition of basal insulin to anti-hyperglycemic agents is insufficient to reach target BG, bolus (prandial) insulin should be added before meals<br>Option exists to only add bolus insulin to the meal with the highest postprandial BG as a starting point<br>Insulin secretagogues typically stopped when bolus (prandial) insulin added; metformin is continued<br>Maintain the basal dose and add bolus insulin with each meal at a dose equivalent to 10% of basal dose<br>Total Daily Insulin (TDI) = 0.3-0.5 U/kg; 40% TDI = basal, 20% TDI = prandial (bolus) prior to each meal<br>Adjust basal insulin to achieve target fasting BG, bolus insulin to achieve postprandial BG levels (5-10 mmol/L) or preprandial BG levels for subsequent meal (4-7 mmol/L) | Dosing and Titration Example<br><br>TDI = 0.5 U/kg: 0.5 x 100 kg = 50 U<br><br>Basal insulin = 40% of TDI<br>40% x 50 U = 20 U; basal bedtime = 20 U<br><br>Bolus insulin = 60% of TDI<br>60% x 50 U = 30 U; 10 U dosed with each meal |
| **Premixed Insulin Before Breakfast and Before Dinner** | |
| Target fasting and pre-dinner BG levels of 4-7 mmol/L<br>Most patients with T2DM need 40-50 U BID to achieve target, but no maximum dose<br>Start at a low dose of 5-10 U BID (before breakfast and before dinner)<br>Patients can self-titrate by increasing insulin dose by 1 U/d until pre-dinner (breakfast dose) or fasting BG (dinner dose) at target<br>Continue metformin and consider stopping secretagogue | Dosing and Titration Example<br><br>10 U ac breakfast, 10 U ac dinner<br><br>Increase breakfast dose by 1 U/d until pre-dinner BG has reached target<br><br>Increase dinner dose by 1 U/d until fasting BG has reached target |

- Correction Factor (CF) = 100/Total Daily Dose of insulin (TDD) = change in blood glucose per unit insulin
  - BG <4: call MD and give 15 g carbohydrates
  - BG between 4 to 8: no additional insulin
  - BG between 8 to (8 + CF): give one additional unit
  - BG between (8 + CF) to (8 + 2CF): give two additional units
  - BG between (8 + 2CF) to (8 + 3CF): give three additional units

## Insulin Pump Therapy: Continuous Subcutaneous Insulin Infusion (CSII)

- external battery-operated device provides continuous basal dose of rapid-acting insulin analogue (aspart, glulisine, or lispro) through small subcutaneous catheter
- at meals, patient programs pump to deliver insulin bolus
- provides improved quality of life and flexibility
- risk of DKA if pump is inadvertently disconnected
- coverage available for insulin pumps for individuals with T1DM varies by province

# Acute Complications

**Table 12. Acute Complications of Diabetes Mellitus: Hyperglycemic Comatose States**

| | Diabetic Ketoacidosis (DKA) | Hyperosmolar Hyperglycemic State (HHS) |
|---|---|---|
| **Pathophysiology** | • Usually occurs in T1DM<br>• Insulin deficiency with ↑ counterregulatory hormones (glucagon, cortisol, catecholamines, GH)<br>• Can occur with lack of insulin (non-adherence, inadequate dosage, 1st presentation) or increased stress (surgery, infection, exercise)<br>• Unopposed hepatic glucose production → hyperglycemia → osmotic diuresis → dehydration and electrolyte disturbance → ↓ $Na^+$ (water shift to ECF causing pseudohyponatremia)<br>• Fat mobilization → ↑ FFA→ ketoacids → metabolic acidosis<br>• Severe hyperglycemia exceeds the renal threshold for glucose and ketone reabsorption → glucosuria and ketonuria<br>• Total body $K^+$ depletion but serum $K^+$ may be normal or elevated, 2º to shift from ICF to ECF due to lack of insulin, ↑ plasma osmolality | • Occurs in T2DM<br>• Often precipitated by sepsis, stroke, MI, CHF, renal failure, trauma, drugs (glucocorticoids, immunosuppressants, phenytoin, diuretics), dialysis, recent surgery, burns<br>• Partial or relative insulin deficiency decreases glucose utilization in muscle, fat, and liver while inducing hyperglucagonemia and hepatic glucose production<br>• Presence of a small amount of insulin prevents the development of ketosis by inhibiting lipolysis<br>• Characterized by hyperglycemia, hyperosmolality, and dehydration without ketosis<br>• More severe dehydration compared to DKA due to more gradual onset and ↑ duration of metabolic decompensation plus impaired fluid intake which is common in bedridden or elderly<br>• Volume contraction → renal insufficiency → ↑ hyperglycemia, ↑ osmolality → shift of fluid from neurons to ECF → mental obtundation and coma |
| **Clinical Features** | • Hyperglycemia (polyuria, polydipsia, weakness)<br>• Acidosis (air hunger, nausea, vomiting, abdominal pain, Kussmaul's respiration, acetone-odoured breath)<br>• Precipitating conditions (insulin omission, new diagnosis of diabetes, infection, MI, thyrotoxicosis, drugs) | • Onset is insidious → preceded by weakness, polyuria, polydipsia<br>• History of decreased fluid intake<br>• History of ingesting large amounts of glucose containing fluids<br>• Dehydration (orthostatic changes)<br>• ↓ LOC → lethargy, confusion, comatose due to high serum osmolality<br>• Kussmaul's respiration is absent unless the underlying precipitant has also caused a metabolic acidosis |
| **Serum** | • ↑ BG (typically 11-55 mmol/L, ↓ $Na^+$ (2º to hyperglycemia → for every ↑ in BG by 10 mmol/L there is a ↓ in $Na^+$ by 3 mmol/L)<br>• Normal or ↑ $K^+$, ↓ $HCO_3^-$, ↑ BUN, ↑ Cr, ketonemia, ↓ $PO_4^{3-}$<br>• ↑ osmolality<br>• corrected sodium = current sodium + [0.3 x (current glucose -5)] | • ↑ BG (typically 44.4-133.2 mmol/L)<br>• In mild dehydration, may have hyponatremia (spurious 2º to hyperglycemia → for every ↑ in BG by 10 mmol/L there is a ↓ in $Na^+$ by 3 mmol/L)<br>– if dehydration progresses, may get hypernatremia<br>• Ketosis usually absent or mild if starvation occurs<br>• ↑ osmolality |
| **ABG** | • Anion Gap Metabolic acidosis with possible 2º respiratory alkalosis<br>• If severe vomiting/dehydration there may also be a metabolic alkalosis | • Metabolic acidosis absent unless underlying precipitant leads to acidosis (e.g. lactic acidosis in MI) |
| **Urine** | • +ve for glucose and ketones | • -ve for ketones unless there is starvation ketosis<br>• Glycosuria |
| **Treatment** | • ABCs are first priority<br>• Monitor degree of ketoacidosis with AG, not BG or serum ketone level<br>• **NOTE: Anion gap is the most important endpoint used to monitor the resolution of the metabolic acidosis**<br>• Rehydration<br>– 500 mL/h x4 h, then 250 mL/h x4 h NS if mild-moderate deficit, 1-2 L/h NS if severe deficit (shock)<br>– Switch to 0.45% NaCl once euvolemic (continue NS if corrected [$Na^+$] is low or rate of fall of plasma osmolality ≥3 mosm/kg/h)<br>– once BG reaches 14.0 mmol/L add D5W or D10W to maintain BG of 12-14 mmol/L<br>• Insulin therapy<br>– critical to resolve acidosis, not hyperglycemia<br>– do not use with hypokalemia (see below), until serum $K^+$ is corrected to >3.3 mmol/L<br>– use only regular insulin (R)<br>– maintain on 0.1 U/kg/h insulin R infusion<br>– check serum glucose hourly<br>• $K^+$ replacement<br>– with insulin administration, hypokalemia may develop<br>– if serum $K^+$<3.3 mmol/L, give 40 mEq/L $K^+$ replacement and hold insulin until [$K^+$] ≥3.3mmol/L<br>– when $K^+$ 3.3-5.0 mmol/L add KCl 10-40 mEq/L to keep $K^+$ in the range of 3.5-5 mEq/L<br>• $HCO_3^-$<br>– if pH <7.0 or if hypotension, arrhythmia, or coma is present give $HCO_3^-$ 1 ampoule (50 mmol) in 200 mL D5W (or sterile water if available) over 1 h, repeated q1-2h until pH ≥7.0<br>– do not give if pH >7.1 (risk of metabolic alkalosis)<br>– can give in case of life-threatening hyperkalemia | • Same resuscitation and emergency measures as DKA<br>• Rehydration<br>– IV fluids: 1 L/h NS initially<br>– evaluate corrected serum $Na^+$<br>– if corrected serum $Na^+$ high or normal, switch to 0.45% NaCl (4-14 mL/kg/h)<br>– if corrected serum $Na^+$ low, maintain NS (4-14 mL/kg/h)<br>– when serum BG reaches 13.9 mmol/L (250 mg/dL) switch to D5W<br>• $K^+$ replacement<br>– less severe $K^+$ depletion compared to DKA<br>– if serum $K^+$ <3.3 mmol/L, give 40 mEq/L $K^+$ replacement and hold insulin until [$K^+$] ≥3.3mmol/L<br>– when $K^+$ 3.3-5.0 mmol/L add KCL 10-40 mEq/L to keep K+ in the range of 3.5-5 mEq/L<br>– if serum $K^+$ ≥5.5 mmol/L, check $K^+$ every 2 h<br>• Search for precipitating event<br>• Insulin therapy<br>– Achieved by monitoring plasma osmolality, adding glucose to infusions once BG reaches 14 mmol/L, using correct concentration of saline<br>– Switch to 0.45% NaCl once euvolemic as urinary loss of electrolytes in osmotic diuresis are usually hypotonic<br>– Increase saline concentration if falling too rapidly |
| **Prognosis** | • <1-3.3% mortality in developed countries<br>• Serious morbidity from sepsis, hypokalemia, respiratory complications, thromboembolic complications, and cerebral edema (the latter in children) | • Mortality rates between 12-17%, but studies looking at this included mixed DKA/HHS state |

# Macrovascular Complications

- increased risk of CAD, ischemic stroke, and peripheral arterial disease secondary to accelerated atherosclerosis
- CAD (see Cardiology and Cardiac Surgery, C25)
  - risk of MI is 3-5x higher in those with DM compared to age-matched controls
  - CAD is the leading cause of death in T2DM
  - most patients with DM are considered "high risk" under the risk stratification for CAD (see *Dyslipidemias*, E2)
- ischemic stroke (see Neurology, N50)
  - risk of stroke in those with DM is approximately 2-3x higher for men and 2-5x higher for women
  - level of glycemia is both a risk factor for stroke and a predictor of a poorer outcome in patients who suffer a stroke
  - HbA1c level is a significant and independent predictor of the risk of stroke
- peripheral arterial disease (see Vascular Surgery, VS2)
  - manifested by intermittent claudication in lower extremities, intestinal angina, foot ulceration
  - risk of foot gangrene is 30x higher in those with DM compared to age-matched controls
  - risk of lower extremity amputation is 15x higher in those with DM
- treatment
  - tight blood pressure control (<130/80 mmHg); especially for stroke prevention
  - tight glycemic control in early DM without established CVD (refer to ACCORD, VADT, ADVANCE, DCCT, EDIC, UKPDS extension studies)
  - tight low density lipoprotein (LDL) cholesterol control (LDL ≤2.0 mmol/L)
  - ACEI or angiotensin receptor blocker in high-risk patients
  - smoking cessation
  - for adults with CVD who do not meet glycemic targets, recommended to add anti-hyperglycemic agent with demonstrated cardiovascular benefit (empagliflozin or liraglutide) to reduce the risk of major cardiovascular events

# Microvascular Complications

## DIABETIC RETINOPATHY (see Ophthalmology, OP33 for a more detailed description)

### Epidemiology
- diabetic retinopathy is the most common cause of incident blindness in people of working age
- among individuals with T1DM, limb amputation and vision loss due to diabetic retinopathy are independent predictors of early death

### Clinical Features
- macular edema: diffuse or focal vascular leakage at the macula
- non-proliferative (microaneurysms, intraretinal hemorrhage, vascular tortuosity, vascular malformation) and proliferative (abnormal vessel growth)
- retinal capillary closure

### Treatment and Prevention
- tight glycemic control (delays onset, decreases progression), tight lipid control, manage HTN, smoking cessation
- ophthalmological treatments available (see Ophthalmology, OP33 for more details)
- annual follow-up visits with an optometrist or ophthalmologist examination through dilated pupils whether symptomatic or not (immediate referral after diagnosis of T2DM; 5 yr after diagnosis of T1DM for those ≥15 yr)
- interval for follow-up should be tailored to severity of retinopathy

## DIABETIC NEPHROPATHY (see Nephrology, NP31 for a more detailed description)

### Epidemiology
- DM-induced renal failure is the most common cause of renal failure in North America
- 20-40% of persons with T1DM (after 5-10 yr) and 4-20% with T2DM have progressive nephropathy

### Screening
- serum creatinine for eGFR, random urine albumin to creatine ratio (ACR)
- ACR is used as albuminuria is considered the earliest clinical sign of diabetic nephropathy (microalbuminuria); diagnosis requires persistent elevated urinary albumin (2 out of 3 urinary samples required over 3 mo)
- 24 h urine collection for protein/albumin is the gold standard but is difficult to perform, inconvenient, and often incorrect; random urine albumin is insufficient as albumin levels vary with urine concentration
- begin screening annually at diagnosis for all T2DM, and >5 yr after diagnosis of T1DM for postpubertal patients



**Laboratory Testing: Ketones**
The nitroprusside test for ketones identifies acetone and acetoacetate but does NOT detect β-hydroxybutyrate (BHB), the ketone most frequently in excess. This has two clinical consequences:
- Be wary of a patient with a clinical picture of DKA but negative serum or urinary ketones. These could be false negatives because of the presence of BHB
- As DKA is treated, BHB is converted to acetone and acetoacetate. Serum or urinary ketones may therefore rise, falsely suggesting that the patient is worsening when in fact they are improving



**Empagliflozin, Cardiovascular Outcomes, and Mortality in T2DM**
NEJM 2015;373:2117-2128
**Purpose**: To examine whether empagliflozin (an SGLT2 inhibitor) has any effect on cardiovascular risk in patients with T2DM.
**Study**: Multi-centre RCT comparing empagliflozin to placebo control; 7020 patients (test N=4687, placebo N=2333), median observation 3.1 yr.
**Outcome**: Death from cardiovascular causes, nonfatal MI, or nonfatal stroke.
**Results**: Both groups concurrently received the standard treatment for T2 DM. The empagliflozin group had significantly lower rates of death from cardiovascular causes than control (3.7%, vs. 5.9%; 38% decreased relative risk). The test group also had lower all-cause mortality (5.7% and 8.3%, respectively; 32% decreased relative risk).
**Conclusion**: Adding empagliflozin to standard treatment for T2DM reduced death from macrovascular complications and all-cause mortality when compared to placebo.



**Liraglutide and Cardiovascular Outcomes in T2DM**
NEJM 2016; 375:311-322
**Purpose**: To investigate whether liraglutide (a GLP-1 analogue) has any effect on cardiovascular risk in patients with T2DM when added to standard care.
**Study**: Multi-centre, double-blind RCT comparing liraglutide to placebo control; 9340 patients (test N=4668, placebo N=4672), median observation 3.8 yr.
**Outcome**: Death from cardiovascular causes, nonfatal MI, or nonfatal stroke.
**Results**: Both groups concurrently received the standard treatment for T2 DM. The liraglutide group had significantly lower rates of death from cardiovascular causes than control (4.7%, vs. 6%; p=0.007). The test group also had lower all-cause mortality (8.2% and 9.6%; p=0.02). Rates of nonfatal MI, nonfatal stroke, and hospitalization for HF were not significantly lower in the liraglutide group.
**Conclusion**: Adding liraglutide to standard treatment for patients with T2DM reduced death from cardiovascular cause and all-cause mortality when compared to placebo.

### Treatment and Prevention
- appropriate glycemic control
- appropriate blood pressure control (<130/80 mmHg)
- use either ACEI or ARB to delay progression of CKD (often used first line for their CVD protection)
- limit use of nephrotoxic drugs and dyes

## DIABETIC NEUROPATHY

### Epidemiology
- approximately 50% of patients within 10 yr of onset of T1DM and T2DM

### Pathophysiology
- can have peripheral sensory neuropathy, motor neuropathy, or autonomic neuropathy
- mechanism poorly understood
- acute cranial nerve palsies and diabetic amyotrophy are thought to be due to ischemic infarction of peripheral nerve
- the more common motor and sensory neuropathies are thought to be related to metabolic, vascular, and perhaps hormonal factors

### Screening
- 128 Hz tuning fork or 10 g monofilament
- begin screening annually at diagnosis for all T2DM, and >5 yr after diagnosis of T1DM for post-pubertal patients

### Clinical Features

**Table 13. Clinical Feature of Diabetic Neuropathies**

| Peripheral Sensory Neuropathy | Motor Neuropathy | Autonomic Neuropathy |
|---|---|---|
| Paresthesias (tingling, itching), neuropathic pain, radicular pain, numbness, decreased tactile sensation<br>Bilateral and symmetric with decreased perception of vibration and pain/temperature; especially true in the lower extremities but may also be present in the hands<br>Decreased ankle reflex<br>Distal-predominant – longest nerves affected first<br>Classic stocking-glove distribution<br>May result in neuropathic ulceration of foot | Less common than sensory neuropathy and occur later in the disease process<br>Delayed motor nerve conduction and muscle weakness/atrophy<br>May involve one nerve trunk (mononeuropathy) or more (mononeuritis multiplex)<br>Some of the motor neuropathies spontaneously resolve after 6-8 wk<br>Reversible CN palsies: III (ptosis/ophthalmoplegia, pupil sparing), VI (inability to laterally deviate eye), and VII (Bell's palsy)<br>Diabetic amyotrophy i.e. Bruns-Garland Syndrome: refers to pain, weakness, and wasting of hip flexors or extensors | Postural hypotension, tachycardia, decreased cardiovascular response to valsalva maneuver<br>Gastroparesis and alternating diarrhea and constipation<br>Urinary retention and erectile dysfunction |

### Treatment and Management
- tight glycemic control
- for neuropathic pain syndromes: tricyclic antidepressants (e.g. amitriptyline), pregabalin, duloxetine, anti-epileptics (e.g. carbamazepine, gabapentin), and capsaicin
- foot care education
- Jobst® fitted stocking and tilting of head of bed may decrease symptoms of orthostatic hypotension
- treat gastroparesis with domperidone and/or metoclopramide (dopamine antagonists), erythromycin (stimulates motilin receptors)
- medical, mechanical, and surgical treatment for erectile dysfunction (see Urology, U33)

# Other Complications

### Dermatologic
- diabetic dermopathy: atrophic brown spots commonly in pretibial region known as "tibia spots", secondary to increased glycosylation of tissue proteins or vasculopathy
- eruptive xanthomas secondary to increased triglycerides
- necrobiosis lipoidica diabeticorum: rare complication characterized by thinning skin over the shins allowing visualization of subcutaneous vessels

### Bone and Joint Disease
- juvenile cheiroarthropathy: chronic stiffness of hand caused by contracture of skin over joints secondary to glycosylated collagen and other connective tissue proteins
- Dupuytren's contracture
- increased fracture risk in both T1DM and T2DM due to increased bone demineralization
- adhesive capsulitis ("frozen shoulder")

**Effect of a Multifactorial Intervention on Mortality in T2DM: The Steno-2 Study**
NEJM 2008;358:580-591
**Study**: Single centre RCT.
**Patients**: People (n=160) with T2DM and persistent microalbuminuria.
**Intervention**: Random assignment to receive either conventional multifactorial treatment or intensified, target-driven therapy involving a combination of medications and focused behaviour modification. Targets included an HbA1c level of <6.5%, a fasting serum total cholesterol level of <4.5 mmol/L, a fasting serum triglyceride level of <1.7 mmol/L, a sBP of <130 mmHg, and a dBP of <80 mmHg. Patients were treated with blockers of the renin–angiotensin system because of their microalbuminuria, regardless of blood pressure, and received low-dose Aspirin® as primary prevention.
**Outcomes**: The primary end point was the time to death from any cause. Other endpoints examined were death from CV causes and various CV events along with diabetic neuropathy, nephropathy, and retinopathy.
**Results**: Twenty-four patients in the intensive-therapy group died, as compared with 40 in the conventional-therapy group (hazard ratio, 0.54; 95% confidence interval [CI] 0.32-0.89; p=0.02). Intensive therapy was associated with a lower risk of death from CV causes (hazard ratio, 0.43; 95% CI 0.19-0.94; p=0.04) and of CV events (hazard ratio, 0.41; 95% CI 0.25-0.67; p<0.001). One patient in the intensive-therapy group had progression to end-stage renal disease, as compared with six patients in the conventional-therapy group (p=0.04). Fewer patients in the intensive-therapy group required retinal photocoagulation (relative risk, 0.45; 95% CI 0.23-0.86; p=0.02).
**Conclusions**: In at-risk patients with T2DM, intensive intervention with multiple drug combinations and behaviour modification had sustained beneficial effects with respect to vascular complications and on rates of death from any cause and from CV causes.

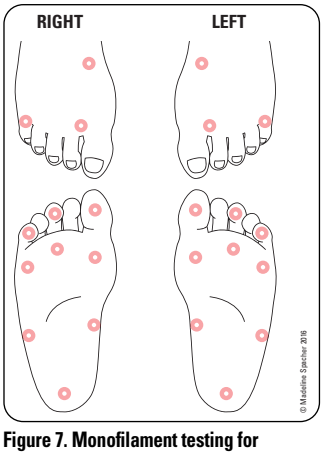



**Figure 7. Monofilament testing for diabetic neuropathy**

**Effects of Treatments for Symptoms of Painful Diabetic Neuropathy: Systematic Review**
BMJ 2007;335:87
**Purpose**: To evaluate the effects of treatments for the symptoms of painful diabetic neuropathy.
**Study Selection**: RCTs comparing topically applied and orally administered drugs with a placebo in adults with painful diabetic neuropathy.
**Results**: 25 included reports compared anticonvulsants (n=1270), antidepressants (94), opioids (329), ion channel blockers (173), NMDA antagonist (14), duloxetine (805), capsaicin (277), and isosorbide dinitrate spray (22) with placebo. The odds ratios in terms of 50% pain relief were 5.33 (95% CI 1.77-16.02) for traditional anticonvulsants, 3.25 (95% CI 2.27-4.66) for newer generation anticonvulsants, and 22.24 (95% CI 5.83-84.75) for tricylic antidepressants. The odds ratios in terms of withdrawals related to adverse events were 1.51 (95% CI 0.33-6.96) for traditional anticonvulsants, 2.98 (95% CI 1.75-5.07) for newer generation anticonvulsants, and 2.32 (95% CI 0.59-9.69) for tricyclic antidepressants.
**Conclusion**: Anticonvulsants and antidepressants are still the most commonly used options to manage diabetic neuropathy. Tricyclic antidepressants and traditional anticonvulsants are better for short-term pain relief than newer anticonvulsants. Evidence of the long-term effects of antidepressants and anticonvulsants is lacking. Further studies are needed on opioids, NMDA antagonists, and ion channel blockers.

### Cataracts
- subcapsular and senile cataracts secondary to glycosylated lens protein or increased sorbitol causing osmotic change and fibrosis

### Infections
- see Infectious Diseases, ID13

## Hypoglycemia

### Etiology and Pathophysiology
- hypoglycemia occurs most frequently in people with DM receiving insulin or certain antihyperglycemic therapies (insulin secretagogues)
- in people without DM, care must be taken to distinguish hypoglycemia that occurs in critically ill or medicated patients from hypoglycemia that presents in individuals who are seemingly well
  - each invokes separate differential diagnoses
  - the timing of hypoglycemia may also provide a clue to the diagnosis (e.g. individuals with an insulinoma typically have fasting hypoglycemia whereas those with noninsulinoma pancreatogenous hypoglycemia experience predominantly postprandial hypoglycemia)

**Table 14. Causes of Hypoglycemia**

| Insulin-Dependent Causes | Insulin-Independent Causes |
|---|---|
| Exogenous insulin<br>Sulfonylurea or meglitinide<br>Pentamidine (possibly due to β-cell destruction resulting in insulin release)<br>Autoimmune hypoglycemia (autoantibodies to insulin or insulin receptor)<br>Insulinoma<br>Non-insulinoma pancreatogenous hypoglycemia<br>Post-gastric bypass hypoglycemia | Hepatic failure<br>Renal failure<br>Inanition<br>Hormone deficiency (cortisol, glucagon and epinephrine in insulin-deficient DM)<br>Non-islet cell tumours (typically the result of mesenchymal tumour overproduction of IGF-II)<br>Inborn error of carbohydrate metabolism, glycogen storage disease, gluconeogenic enzyme<br>Alcohol<br>Drugs (e.g. quinine, indomethacin, gatifloxacin, lithium, ACE inhibitors, β-adrenergic receptor blockers) |

### Clinical Features
- Whipple's triad – suggest a patient's symptoms are from hypoglycemia
  1. serum glucose <4.0 mmol/L
  2. neuroglycopenic symptoms (below)
  3. rapid relief provided by administration of glucose
- autonomic symptoms (typically occur first; caused by autonomic nervous system activity)
  - palpitations, sweating, anxiety, tremor, tachycardia, hunger
- neuroglycopenic symptoms (caused by brain glucose deprivation)
  - dizziness, headache, clouding of vision, mental dullness, fatigue, confusion, seizures, coma

### Investigations
- depend on a thorough history, physical exam, and available biochemical investigations as these may provide clues to the etiology of hypoglycemia
  - for example, if suspecting insulin and insulin secretagogues in patients with diabetes, assess for cortisol deficiency. In a patient with weight loss, hyperpigmentation, and hyperkalemia, consider the possibility of IGF-2 mediated hypoglycemia. In an individual with a gastrointestinal stromal tumour (GIST), think about renal/hepatic failure in the setting of critical illness
- when the cause of hypoglycemia is not evident, screen for oral hypoglycemic agents and measure plasma glucose, serum ketones, insulin, pro-insulin, C-peptide, and insulin antibodies during a spontaneous hypoglycemic episode or a supervised fast of up to 72 h. If hypoglycemia occurs only in the postprandial state, evaluate the patient first with a mixed meal test

### Treatment
- for tumoural hypoglycemia, definitive treatment requires resection of the tumour. If that is not possible certain medications can be helpful such as diazoxide for patients with insulinoma
  - for noninsulinoma pancreatogenous hypoglycemia and post-bariatric bypass hypoglycemia, dietary changes including reducing the amount of carbohydrate intake and small frequent meals may be helpful. For patients who do not respond to nutritional modification or have severe symptoms acarbose can be utilized
- see Emergency Medicine, ER35
- treatment of hypoglycemic episode in the unconscious patient or patient NPO
  - D50W 50 mL (1 ampule) IV in 1-3 min or 1 mg glucagon SC or IM (if no IV access is available)
  - may need ongoing glucose infusion once BG >5 mmol/L



**Other Players in Glucose Homeostasis**
These hormones act to increase blood glucose levels
- Glucagon
- Epinephrine
- Cortisol
- Growth hormone



**C-Peptide**
A short peptide released into the circulation when proinsulin is cleaved to insulin



**Use C-peptide Levels to Distinguish between Exogenous and Endogenous Source of Hyperinsulinemia**
Increased = endogenous
Decreased or normal = exogenous



**Treatment of Acute Hypoglycemic Episode (Blood Glucose <4.0 mmol/L) in the Awake Patient (e.g. able to self-treat)**

1) Eat 15 g of carbohydrates (CHO) (e.g. 3 packets sugar dissolved in water; 3/4 cup of juice)
↓
2) Wait 15 min
↓
3) Retest Blood Glucose (BG)
↓
4) Repeat steps 1-3 until BG >5 mmol/L
↓
5) Eat next scheduled meal. If next meal is >1 h away, eat snack including 15 g of CHO and protein



**Hypoglycemia Unawareness (T1DM >>> T2DM)**
- Patient remains asymptomatic until severely hypoglycemic levels are reached
- **Causes**:
  - Decreased glucagon/epinephrine response
  - History of repeated hypoglycemia or low HbA1c
  - Autonomic neuropathy
- Not safe for patient to drive
- Suggest that patient obtain a Medic-Alert bracelet if at risk for hypoglycemia, especially with hypoglycemia unawareness



**5 to Drive**
BG must be >5 mmol/L to drive

# Metabolic Syndrome

- postulated syndrome related to insulin resistance associated with hyperglycemia, hyperinsulinemia, HTN, central obesity, and dyslipidemia
- obesity aggravates extent of insulin resistance
- complications include DM, atherosclerosis, CAD, MI, and stroke
- women with PCOS are at increased risk for developing insulin resistance, hyperlipidemia, and metabolic syndrome
- not to be confused with syndrome X related to angina pectoris with normal coronary arteries (Prinzmetal angina)

# Obesity

- see Family Medicine, FM7

# Pituitary Gland

## Pituitary Hormones

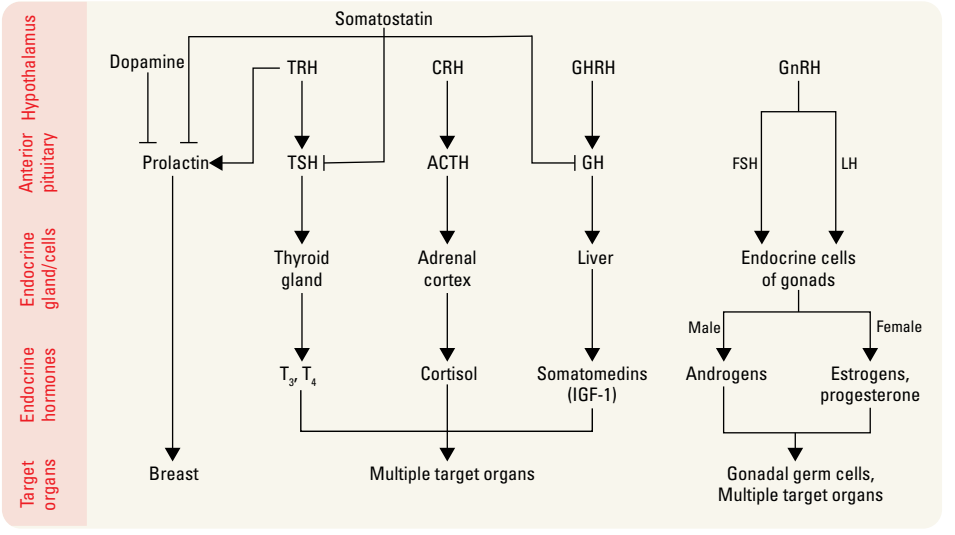



**Figure 8. Hypothalamic-pituitary hormonal axes**
CRH = corticotropin-releasing hormone; GHRH = growth hormone-releasing hormone; GnRH = gonadotropin-releasing hormone; PRH = prolactin-releasing hormone; TRH = thyrotropin-releasing hormone

### Hypothalamic Control of Pituitary

- trophic and inhibitory factors control the release of pituitary hormones
- most hormones are primarily under trophic stimulation except prolactin, which is primarily under inhibitory control by dopamine. GH and TSH are stimulated by GHRH and TRH respectively; less important for control is their inhibition by somatostatin
- transection of the pituitary stalk (i.e. dissociation of hypothalamus and pituitary) leads to pituitary hypersecretion of prolactin and hyposecretion of all remaining hormones

### Anterior Pituitary Hormones

- follicle stimulating hormone (FSH), luteinizing hormone (LH), adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), prolactin, growth hormone (GH)

### Posterior Pituitary (Hypothalamic) Hormones

- antidiuretic hormone (ADH) and oxytocin
- peptides synthesized in the supraoptic and paraventricular nuclei of the hypothalamus
- although ADH and oxytocin are produced in the hypothalamus, these hormones are stored, and released from the posterior pituitary

**Features of Metabolic Syndrome (≥3 measures to make a Dx)**

| Measure | Men | Women |
|---|---|---|
| Abdominal Obesity (Elevated Waist Circumference | | |
| Canada, USA | ≥102 cm (40 inches) | ≥88 cm (35 inches) |
| Europid, Middle Eastern, Sub-Saharan Africa, Mediterranean | ≥94 cm (37 inches) | ≥80 cm (31.5 inches) |
| Asian, Japanese, South & Central America | ≥90 cm (35 inches) | ≥80 cm (31.5 inches) |
| Triglyceride Level | ≥1.7 mmol/L (150 mg/dL) | |
| HDL-C Level | <1.0 mmol/L (<40 mg/dL) | <1.3 mmol/L (<50 mg/dL) |
| Blood Pressure | ≥130/85 mmHg | |
| Fasting Glucose Level | ≥5.6 mmol/L (>100 mg/dL) | |

Drug treatment for any elevated marker is an alternate indicator

**Anterior Pituitary Hormones**
**"FLAT PiG"**
**F**SH
**L**H
**A**CTH
**T**SH

**P**rolactin
**G**H

**Table 15. The Physiology and Action of Pituitary Hormones**

| Hormone | Function | Physiology | Inhibitory Stimulus | Secretory Stimulus |
|---|---|---|---|---|
| **LH/FSH** | Stimulate gonads via cAMP<br>Ovary:<br>LH: production of androgens (thecal cells) which are converted to estrogens (granulosa cells); induces luteinization in follicles<br>FSH: growth of granulosa cells in ovarian follicle; controls estrogen production<br>Testes:<br>LH: production of testosterone (Leydig cells)<br>FSH: production of spermatozoa (Sertoli cells) | Polypeptide<br>Glycoproteins (similar α subunit as TSH and hCG)<br>Secreted in pulsatile fashion | Estrogen<br>Progesterone<br>Testosterone<br>Inhibin<br>Continuous (i.e. non-pulsatile) GnRH infusion | Pulsatile GnRH (low frequency pulsation = FSH release, high frequency pulsation = LH release) |
| **ACTH** | Stimulates growth of adrenal cortex and secretion of its hormones | Polypeptide<br>Pulsatile and diurnal variation (highest in AM, lowest at midnight) | Dexamethasone, cortisol, and other glucocorticoids | CRH<br>Metyrapone<br>Insulin-induced hypoglycemia<br>Vasopressin<br>Fever, pain, stress |
| **TSH** | Stimulates growth of thyroid and secretion of $T_3$ and $T_4$ via cAMP | Glycoprotein<br>Note: hCG can act like TSH and react with TSH receptor | Thyroid hormones ($T_3$, $T_4$) and analogues, dopamine, somatostatin, cytokines, high dose glucocorticoids | TRH<br>AVP<br>α adrenergic agonist |
| **Prolactin** | Promotes milk production<br>Inhibits GnRH secretion | Polypeptide<br>Episodic secretion | Dopamine (only pituitary hormone under tonic inhibition of secretion) | Sleep<br>Stress, hypoglycemia<br>Pregnancy, breastfeeding<br>Mid-menstrual cycle<br>Sexual activity<br>TRH<br>Drugs: antipsychotics, tricyclic antidepressants, metoclopramide, domperidone, verapamil, methyldopa, opioids, high dose estrogen |
| **GH** | Needed for linear growth<br>Stimulates secretion of IGF-1, a potent growth and differentiation factor | Polypeptide<br>Acts indirectly through IGF-1 (somato-medin-C) synthesized in the liver<br>Only anterior pituitary hormone that also acts directly on peripheral target cells<br>Serum GH undetectable for most of the day and suppressed after meals high in glucose<br>Sustained rise during sleep | Glucose challenge<br>Glucocorticoids<br>Somatostatin<br>Dopamine D2 receptor agonists<br>IGF-1 (long-loop) | GHRH<br>Insulin-induced hypoglycemia<br>Ghrelin<br>Exercise<br>REM sleep<br>Arginine, clonidine, propranolol, L-dopa<br>Sex hormones |
| **ADH** | Acts at renal collecting ducts on V2 receptors to cause insertion of aquaporin channels and increases water reabsorption thereby concentrating urine | Octapeptide<br>Secreted by posterior pituitary<br>Osmoreceptors in hypothalamus detect serum osmolality<br>Contracted plasma volume detected by baroreceptors is a more potent stimulus than ↑ osmolality | ↓ serum osmolality | Hypovolemia or ↓ effective circulatory volume<br>↑ serum osmolality<br>Stress, pain, fever, paraneoplastic<br>Lung or brain pathology |
| **Oxytocin** | Causes uterine contraction<br>Breast milk secretion | Nonapeptide<br>Secreted by posterior pituitary | EtOH | Suckling<br>Distention of female genital tract during labour via stretch receptors |

# Growth Hormone

## GH DEFICIENCY

- cause of short stature in children (see Pediatrics, P28)
- adults exhibit increased fat and decreased lean body mass, decreased bone mineral density, and fatigue
- diagnosis made with low serum IGF-1 levels in individuals with pituitary or hypothalamic disease or by failure to increase GH with a provocative test (see above under GH secretory stimulus)
- Tx: GH replacement if adult patient with childhood onset GH deficiency, and some patients with adult onset GH deficiency

### GH EXCESS

#### Etiology
- GH secreting pituitary adenoma, neuroendocrine tumours secreting ectopic GH or GHRH (very rare)

#### Pathophysiology
- normally GH is a catabolic hormone that acts to increase blood glucose levels
- in GH excess states, secretion remains pulsatile but there is loss of hypoglycemic stimulation, glucose suppression, and the nocturnal surge
- proliferation of bone, cartilage, soft tissues, organomegaly
- insulin resistance and impaired glucose tolerance (IGT)

#### Clinical Features
- in children (before epiphyseal fusion) leads to gigantism
- in adults (after epiphyseal fusion) leads to acromegaly
- dermatologic (thickening of skin, increased sebum production, sweating, acne, sebaceous cysts), musculoskeletal (enlargement of hands and feet, coarsening of facial features, thickening of calvarium, prognathism, carpal tunnel syndrome, osteoarthritis), cardiac/metabolic (HTN, DM, acanthosis nigricans, cardiomyopathy), sleep apnea, sexual (low libido)

#### Investigations
- first line test: serum IGF-1 (expected to be elevated)
- glucose suppression test is the most specific test (75 g of glucose PO suppresses GH levels in healthy individuals but not in patients with acromegaly)
- CT, MRI, or skull x-rays may show cortical thickening, enlargement of the frontal sinuses, and enlargement and erosion of the sella turcica
- MRI of the sella turcica is needed to look for a tumour

#### Treatment
- surgery, octreotide (somatostatin analogue), dopamine agonist (cabergoline), GH receptor antagonist (pegvisomant), radiation

**Risks Associated with GH Excess**
- Cardiac disease (e.g. CAD, cardiomegaly, cardiomyopathy) in 1/3 of patients, with a doubling of risk of death from cardiac disease
- HTN in 1/3 of patients
- Risk of cancer (particularly GI) increased 2-fold to 3-fold

## Prolactin

### HYPERPROLACTINEMIA

#### Etiology
- prolactinoma: most common pituitary adenoma (prolactin-secreting tumours may be induced by estrogens and grow during pregnancy)
- pituitary masses with pituitary stalk compression causing reduced dopamine inhibition of prolactin release
- primary hypothyroidism (increased TRH)
- decreased clearance due to chronic renal failure or severe liver disease (prolactin is metabolized by both the kidney and liver)
- medications with anti-dopaminergic properties are a common cause of high prolactin levels: antipsychotics (common), antidepressants, antihypertensives (verapamil/methyldopa), anti-migraine agents (triptans/ergotamines), bowel motility agents (metoclopramide/domperidone), H2-blockers (ranitidine)
- macroprolactinemia (high molecular weight prolactin also known as big-big prolactin) that has no action

#### Clinical Features
- galactorrhea (secretion of breast milk in women and, in rare cases, men), infertility, hypogonadism, amenorrhea, oligomenorrhea, erectile dysfunction

#### Investigations
- serum PRL, TSH, liver enzyme tests, creatinine
- macroprolactin level in patients with hyperprolactinemia but no symptoms of prolactin excess
- MRI of the sella turcica when a secondary cause is not identified or when prolactin levels suggest that there may be underlying tumoural hyperprolactinemia

#### Treatment
- first line: long-acting dopamine agonist: bromocriptine, cabergoline, or quinagolide
- surgery ± radiation (rare)
- prolactin-secreting tumours are often slow-growing; treatment may not be necessary in the setting of small tumours associated with hyperprolactinemia that does not result in hypogonadism or bothersome galactorrhea
- if medication-induced, consider stopping medication if possible
- in certain cases if microprolactinoma and not planning on becoming pregnant, may consider OCP

**Approach to Nipple Discharge**
- Differentiate between galactorrhea (fat droplets present) versus breast discharge (usually unilateral, may be bloody or serous)
- If galactorrhea, determine if physiologic (e.g. pregnancy, lactation, stress) versus pathologic
- If abnormal breast discharge, must rule out a breast malignancy

## Thyroid Stimulating Hormone

- see *Thyroid*, E21

# Adrenocorticotropic Hormone

- see *Adrenal Cortex*, E30

# Luteinizing Hormone and Follicle Stimulating Hormone

## HYPOGONADOTROPIC HYPOGONADISM

- hypogonadism due to impaired release of FSH and LH

### Etiology

- primary/congenital: Kallmann syndrome, CHARGE syndrome, GnRH insensitivity
- secondary: CNS or pituitary tumours, pituitary apoplexy, brain/pituitary radiation, drugs (GnRH agonists/antagonists, glucocorticoids, narcotics, chemotherapy, drugs causing hyperprolactinemia), functional deficiency due to another cause (hyperprolactinemia, chronic systemic illnesses, eating disorders, hypothyroidism, DM, Cushing's disease), systemic diseases (hemochromatosis, sarcoidosis, histiocytosis)

### Clinical Features

- hypogonadism, amenorrhea, erectile dysfunction (see Urology, U32), loss of body hair, fine skin, testicular atrophy, and failure of pubertal development

### Treatment

- combined FSH/LH hormone therapy, human chorionic gonadotropin (hCG), rFSH, or pulsatile GnRH analogue if fertility desired
- symptomatic treatment with estrogen/testosterone

## HYPERGONADOTROPIC HYPOGONADISM

- hypogonadism due to impaired response of the gonads to FSH and LH

### Etiology

- congenital:
  - chromosomal abnormalities (Turner's syndrome, Klinefelter syndrome, XX gonadal dysgenesis)
  - enzyme defects (17α-hydroxylase deficiency, 17,20-lyase deficiency)
  - gonadotropin resistance (Leydig cell hypoplasia, FSH insensitivty, pseudohypoparathyroidism type 1A)
- acquired:
  - gonadal toxins (chemotherapy, radiation)
  - drugs (glucocorticoids, antiandrogens, opioids, alcohol)
  - infections (STIs, mumps)
  - gonadal failure in adults (androgen decline and testicular failure in men, premature ovarian failure and menopause in women)

### Clinical Features

- amenorrhea, erectile dysfunction (see Urology, U33), loss of body hair, fine skin, testicular atrophy, failure of pubertal development, low libido, and infertility

### Treatment

- hormone replacement therapy consisting of androgen (for males) and estrogen (for females) administration

# Antidiuretic Hormone

## DIABETES INSIPIDUS

### Definition

- disorder of ineffective ADH (decreased production or peripheral resistance) resulting in passage of large volumes of dilute urine

### Etiology and Pathophysiology

- central DI: insufficient ADH due to pituitary surgery, tumours, idiopathic/autoimmune, stalk lesion, hydrocephalus, histiocytosis X, trauma, familial central DI
- nephrogenic DI: collecting tubules in kidneys resistant to ADH due to drugs (e.g. lithium), hypercalcemia, hypokalemia, chronic renal disease, hereditary nephrogenic DI
- psychogenic polydipsia and osmotic diuresis must be ruled out



**Diagnosing Subtypes of DI with DDAVP Response**
**C**oncentrated urine = **C**entral
**N**o effect = **N**ephrogenic

### Clinical Features

- passage of large volumes of dilute urine, polydipsia, and dehydration; hypernatremia can develop with inadequate water consumption or secondary to an impaired thirst mechanism

### Diagnostic Criteria

- fluid deprivation will differentiate true DI (high urine output persists, urine osmolality < plasma osmolality) from psychogenic DI (psychogenic polydipsia)
- response to exogenous ADH (DDAVP) will distinguish central from nephrogenic DI

### Treatment
- central DI: first line = desmopressin; second line = chlorpropamide, thiazides, NSAIDs and carbamazepine
- nephrogenic DI: solute restriction, thiazide diuretics

## SYNDROME OF INAPPROPRIATE ADH SECRETION

### Diagnostic Criteria
- 1) hyponatremia (serum $Na^+$ <135 mEq/L) with 2) plasma hypo-osmolality (<275 mOsm/kg), 3) urine $Na^+$ concentration >40 mEq/L, 4) urine osmolality >100 mOsm/kg), 5) euvolemia (no edema) and 6) absence of adrenal, renal, or thyroid insufficiency

### Etiology and Pathophysiology
- stress (pain, nausea, post-surgical)
- malignancy (lung, pancreas, lymphoma)
- CNS disease (inflammatory, hemorrhage, tumour, Guillain-Barré syndrome)
- respiratory disease (tuberculosis, pneumonia, empyema)
- drugs (SSRIs, vincristine, chlorpropamide, cyclophosphamide, carbamazepine, nicotine, morphine, DDAVP, oxytocin)

### Clinical Features
- symptoms of hyponatremia: headaches, nausea, vomiting, muscle cramps, tremors, cerebral edema if severe (confusion, mood swings, hallucinations, seizures, coma)

### Treatment
- goal is to increase serum sodium
- treat underlying cause, fluid restriction (800-1000 mL/d), vasopressin receptor antagonists (e.g. tolvaptan, conivaptan), demeclocycline (antibiotic with anti-ADH properties, rarely-used), and furosemide

**SIADH vs. Cerebral Salt Wasting (CSW)**
CSW can occur in cases of subarachnoid hemorrhage. $Na^+$ is excreted by malfunctioning renal tubules, mimicking findings of SIADH; hallmark is hypovolemia

# Pituitary Pathology

## PITUITARY ADENOMA (see Neurosurgery, NS14)

### Clinical Features
- local mass effects
  - visual field defects (bitemporal hemianopsia due to compression of the optic chiasm), diplopia (due to oculomotor nerve palsies is rare), headaches; increased ICP is rare
- hypofunction
  - hypopituitarism
- hyperfunction
  - PRL (galactorrhea), GH (acromegaly in adults, gigantism in children), ACTH (Cushing's disease = Cushing's syndrome caused by a pituitary tumour)
  - tumours secreting LH, FSH, and TSH are rare

### Investigations
- radiological evaluation (MRI is imaging procedure of choice)
- formal visual field testing for tumours compressing the optic chiasm
- hypothalamic-pituitary hormonal function

**Important Deficiencies to Recognize are:**
- Adrenal insufficiency
- Hypothyroidism

Concurrent adrenal insufficiency and hypothyroidism should be treated with glucocorticoids first and then with thyroid hormone to avoid adrenal crisis

**The Pituitary Hormones**
Order they are usually lost with compression by a mass:
"**G**o **L**ook **F**or **T**he **A**denoma **P**lease"
**G**H, **L**H, **F**SH, **T**SH, **A**CTH, **P**RL + posterior pituitary hormones: ADH and oxytocin

## HYPOPITUITARISM

### Etiology (The Eight I's)
- **I**nvasive
  - pituitary tumours, craniopharyngioma, cysts (Rathke's cleft, arachnoid, or dermoid), metastases
- **I**nfarction/hemorrhage
  - Sheehan's syndrome (pituitary infarction due to excessive post-partum blood loss and hypovolemic shock)
  - pituitary apoplexy (acute hemorrhage/infarction of a pituitary tumour; presents with sudden loss of pituitary hormones, severe headache, and altered level of consciousness; can be fatal if not recognized and treated early)
- **I**nfiltrative/inflammatory
  - sarcoidosis, hemochromatosis, histiocytosis
- **I**nfectious
  - syphilis, tuberculosis, fungal (histoplasmosis), parasitic (toxoplasmosis)
- **I**njury
  - severe head trauma
- **I**mmunologic
  - autoimmune destruction
- **I**atrogenic
  - following surgery or radiation
- **I**diopathic
  - familial forms, congenital midline defects

### Clinical Features
- symptoms depend on which hormone is deficient:
  - ACTH: fatigue, weight loss, hypoglycemia, anemia, hyponatremia, failure to thrive and delayed puberty in children
  - GH: short stature in children, adults exhibit increased fat and decreased lean body mass, decreased BMD, fatigue
  - TSH: tiredness, cold intolerance, constipation, weight gain
  - LH and FSH: oligo- or amenorrhea, infertility, decreased facial/body hair and muscle mass in men, erectile dysfunction, delayed puberty
  - Prolactin: inability to breastfeed
  - ADH: symptoms of diabetes insipidus (extreme thirst, polydipsia, hypernatremia)
  - Oxytocin: usually asymptomatic – only needed during labour and breastfeeding

### Investigations
- triple bolus test
  - stimulates release of all anterior pituitary hormones in normal individuals
  - rapid sequence of IV infusion of insulin, GnRH, and TRH
  - insulin (usual dose 0.1 unit/kg of human regular insulin) → hypoglycemia → increased GH and ACTH/cortisol
  - GnRH (100 μg IV push) → increased LH and FSH
  - TRH (200 μg IV push over 120 s) → increased TSH and PRL (no longer available in Canada)
  - GnRH and TRH stimulation tests are very limited in their utility; the insulin tolerance test is the only truly useful test in the triple bolus assessment

# Thyroid

## Thyroid Hormones

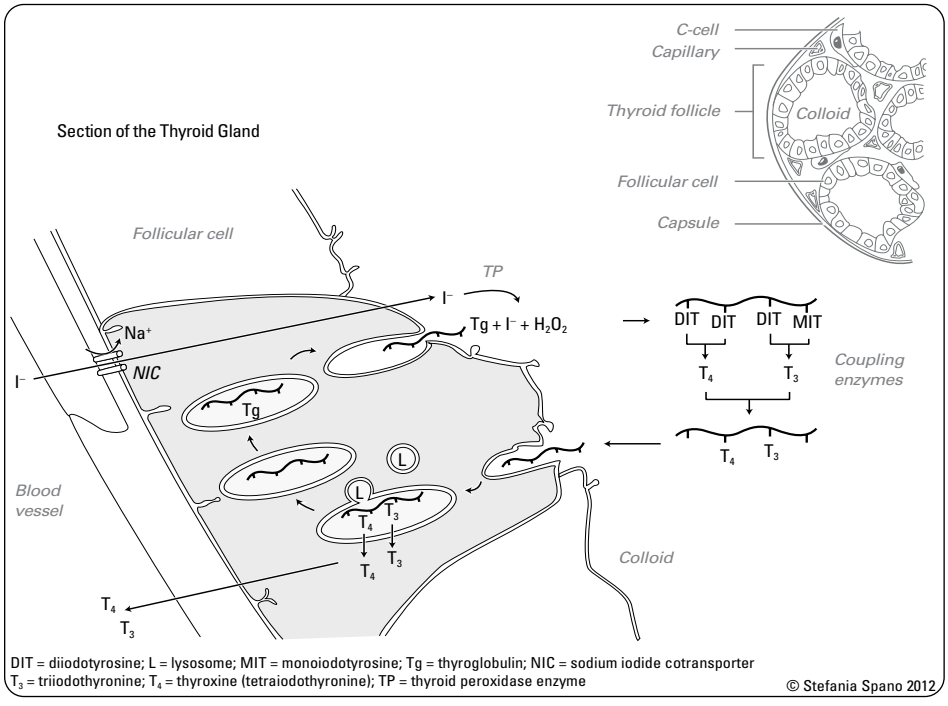



**Figure 9. Thyroid hormone synthesis**

### Synthetic Function of Thyroid Gland
- the synthesis of thyroid hormones $T_4$ (thyroxine) and $T_3$ (triiodothyronine) by the thyroid gland involves trapping and oxidation of iodide, iodination of thyroglobulin, proteolysis of thyroglobulin, and release of $T_3$ and $T_4$
  - more than 90% of thyroid hormone secreted by the thyroid is $T_4$
- free $T_4$ (0.02%) and free $T_3$ (0.3%) represent the hormonally active fraction of thyroid hormones
  - the remaining fraction is bound to thyroxine binding globulin (TBG), albumin and transthyretin, and is biologically inactive
- $T_3$ is more biologically active (approximately 4x as potent as $T_4$), but $T_3$ is present in the blood in smaller quantities and has a shorter half-life compared to $T_4$
- 85% of $T_4$ is converted to $T_3$ or reverse $T_3$ ($RT_3$) in the periphery by deiodinase enzymes
- $RT_3$ is metabolically inactive but produced in times of stress to decrease metabolic activity

**Extra-Thyroidal Factors Impacting Thyroid Hormone Homeostasis: A Review**
JRM 2015;4(1):40-49
- Most peripheral thyroid metabolism occurs in the liver and the kidneys, thus severe liver disease and CKD can significantly alter $T_3$:$T_4$ ratio.
- Alcohol dependence results in hypothalamic-pituitary-thyroid axis dysfunction demonstrated by decreased TSH, $T_4$, and $T_3$ levels.
- Smoking is associated with lower TSH levels in a dose-dependent manner: with heavy smoking (8-12 cigarettes/d) having more TSH suppression than light smokers (<4 cigarettes/d).
- Heavy metal exposure including lead, mercury, and cadamium has been shown to alter thyroid hormone function and peripheral metabolism.

**Patterns of Hormone Levels**

| | TSH | $T_3$, $T_4$ |
|---|---|---|
| 1° Hyper | ↓ | ↑ |
| 2° Hyper | ↑ | ↑ |
| 1° Hypo | ↑ | ↓ |
| 2° Hypo | ↓ | ↓ |

- most of the plasma T3 pool is derived from the peripheral conversion of $T_4$
- calcitonin, a peptide hormone, is also produced in the thyroid, by the parafollicular cells or C cells
  - calcitonin functions by inhibiting osteoclast activity and increasing renal calcium excretion

### Role of Thyroid Hormones

- thyroid hormones act primarily through modifying gene transcription by binding to nuclear receptors
- action of these hormones is diffuse, affecting nearly every organ system
- thyroid hormones have different tissue-specific effects determined by the expression of the types of thyroid receptor isoform and the local production of $T_3$
- they increase the basal metabolic rate including: increased $Na^+/K^+$ ATPase activity, increased $O_2$ consumption, increased respiration, heat generation, and increased cardiovascular activity
- when present at higher than normal levels it potentiates the actions of GH, catecholamines (epinephrine, norepinephrine), glucagon and cortisol, resulting in increased gluconeogenesis, ketogenesis and proteolysis, mimicking what happens in starvation
- it increases sensitivity to catecholamines, by up-regulating their receptors, but does not alter their blood concentrations
- thyroid hormone is required for normal growth in the fetus and child, including the central nervous system, via stimulation of GH release, in synergism with cortisol

### Regulation of Thyroid Function

- extrathyroid
  - stimulation of thyroid by TSH, epinephrine, prostaglandins (cAMP stimulators $T_3$ negatively feeds back on anterior pituitary to inhibit TSH and on hypothalamus to inhibit TRH
- $T_3$ intrathyroid (autoregulation)
  - synthesis (Wolff-Chaikoff effect, Jod-Basedow effect)
  - there is varying thyroid sensitivity to TSH in response to iodide availability
  - increased ratio of $T_3$ to $T_4$ in iodide deficiency
  - increased activity of peripheral 5' deiodinase in hypothyroidism increases $T_3$ production despite low $T_4$ levels

## Tests of Thyroid Function and Structure

### TSH

- third generation TSH is the best test for assessing thyroid function
- hyperthyroidism
  - primary: TSH is low because of negative feedback from increased levels of circulating $T_3$ and $T_4$
  - secondary: increased TSH results in increased $T_3$ and $T_4$
- hypothyroidism
  - primary: increased TSH (most sensitive test) because of less negative feedback from $T_3$ and $T_4$
  - secondary: TSH is low or normal with variable response to TRH depending on the site of the lesion (pituitary or hypothalamic)

### Free $T_3$ and Free $T_4$

- standard assessment of thyroid function measures TSH and, if necessary, free $T_4$. Free $T_3$ should only be measured in the small subset of patients with hyperthyroidism and suspected $T_3$ toxicosis. TSH would be suppressed, free $T_4$ normal, and free $T_3$ elevated

### Thyroid Autoantibodies

- thyroglobulin antibodies (TgAb), anti-thyroid peroxidase antibodies (TPOAb), and TSH receptor antibodies (TRAb) of the blocking variety are increased in Hashimoto's disease; normal variant in 10-20% of individuals
- TRAb of the stimulating variety are also referred to as thyroid stimulating immunoglobulins (TSI) and cause Graves' disease. However, both TRAb receptor blocking and stimulating antibodies are seen in patients with Graves' disease

### Plasma Thyroglobulin

- used to monitor for residual thyroid tissue post-thyroidectomy, e.g. tumour marker for thyroid cancer recurrence
- detectable or elevated levels may suggest persistent, recurrent, or metastatic disease

### Serum Calcitonin

- not routinely done to investigate thyroid nodules
- ordered if suspicion of medullary thyroid carcinoma e.g. in patients with a thyroid nodule and suspected or confirmed MEN IIa or IIb syndromes or those who have a pathogenic mutation in RET
- used to monitor for residual or recurrent medullary thyroid cancer



**Thyroid Assessment**

- Serum thyroid hormones (TSH, $T_3$, $T_4$)
- Antibodies (TRAb, TgAb and TPOAb)
- Thyroglobulin (to monitor thyroid cancer)
- Thyroid ultrasound
- Nuclear uptake and scan (for hyperthyroidism)
- Biopsy (FNA)



**Does this Patient have a Goitre?**
**From The Rational Clinical Examination**
JAMA 2009; https://jamaevidence.mhmedical.com/content.aspx?bookid=845&sectionid=61357508

**Study**: Systematic review of articles assessing the accuracy and precision of the clinical exam in the diagnosis of a goitre.

**Results**: Clinical diagnosis was based on degree of lateral prominence, visibility, and palpability of the thyroid gland. No evidence exists to support the superiority of any one method.

The combined results of 4 studies detail the predictive utility of assessing grades of thyroid gland weight:

| Weight | Reference | LR+ | 95% CI |
|---|---|---|---|
| 0-20 g | normal | 0.15 | (0.10-0.21) |
| 20-40 g | 1-2x | 1.9 | (1.1-3.0) |
| >40 g | >2x | 25.0 | (2.6-175) |

Alternatively, defining a goitre as mass larger than the distal phalanx of the thumb has been shown to have an LR+ of 3.0 (95% CI 2.5-3.5) and LR- of 0.30 (95% CI 0.24-0.37) in children, and an LR+ of 4.7 (95% CI 3.6-6.0) and LR- of 0.08 (95% CI 0.02-0.27) for the presence of a goitre.

**Conclusions**: Use of weight of thyroid tissue is an appropriate method of diagnosing a goitre, while comparing the size of thyroid mass to the distal phalanx of the thumb may be a useful alternative.

### Thyroid Imaging/Scans

- normal gland size 15-20 g (estimated by palpation)
- thyroid U/S
  - to measure size of gland, characterize thyroid nodules, facilitate fine needle aspirate biopsy (FNAB)
  - ultrasonography is the first line tool for identification of thyroid nodules that require FNAB; exception is hyperthyroid patients with thyroid nodules where use of a radioisotope thyroid scan and RAIU (see below) permits identification of hyperfunctioning nodules which generally do not need to be biopsied
- radioisotope thyroid scan (Technetium-99) only if 1) one or more thyroid nodule(s) and 2) patient is hyperthyroid to determine whether nodules are hot (functioning → excess thyroid hormone production) or cold (non-functioning)
- hot nodule → very low chance malignancy; treat hyperthyroidism
- cold nodule →further workup required (U/S, then FNAB if concerning sonographic features)
- radioactive iodine uptake (RAIU)
  - test of function: order if patient is thyrotoxic
  - RAIU measures the turnover of iodine by thyroid gland *in vivo*
  - if ↑ uptake (e.g. incorporated), gland is overactive (hyperthyroid)
  - if ↓ uptake (e.g. not incorporated), gland is leaking thyroid hormone (e.g. thyroiditis), exogenous thyroid hormone use, or excess iodine intake (e.g. amiodarone or contrast dye, which has high iodine content)
- see Figure 9, *Thyroid Hormone Synthesis*, E21 for further information regarding the utility of these scans

### Thyroid Biopsy

- fine needle aspiration (FNA) for cytology
  - differentiates between benign and malignant disease
  - best done under U/S guidance
  - accuracy decreased if nodule is greater than 50% cystic, or if nodule located posteriorly in the gland

**Table 16. Summary of Diagnostic Testing in Hyperthyroidism and Hypothyroidism**

| | Hyperthyroidism | Hypothyroidism |
|---|---|---|
| **TSH** | Decreased in 1° hyperthyroidism<br>Increased in 2° hyperthyroidism | Increased in 1° hypothyroidism<br>Decreased in 2° hypothyroidism |
| **Free $T_4$** | Increased in 1° hyperthyroidism<br>Increased in 2° hyperthyroidism | Decreased in 1° hypothyroidism<br>Decreased in 2° hypothyroidism |
| **Antibodies** | Graves': TRAb (thyroid receptor antibody) | Hashimoto's: antithyroid peroxidase, thyroglobulin (TPOAb, TgAb) |
| **RAIU** | Increased uptake<br>Graves'<br>Toxic multinodular goitre<br>Toxic adenoma<br>Decreased uptake<br>Subacute thyroiditis<br>Recent iodine load<br>Exogenous thyroid hormone | |
| **Radioisotope Thyroid Scan** | Graves': homogenous diffuse uptake<br>Multinodular goitre: heterogeneous uptake<br>Toxic adenoma: single intense area of uptake with suppression elsewhere | |

**Drugs Affecting Thyroid Function**

Thyroid 2010;20(7):763-770

- Lithium plays an inhibitory role in thyroid hormone release, resulting in clinical hypothyroidism and goitre.
- **Amiodarone-Induced Hypothyroidism** (AIH): Amiodarone, a class III anti-arrhythmic drug, contains 2 atoms of iodine per molecule and is structurally similar to thyroid hormones, and may exert antagonistic effects on TSH receptors. It is also shown to inhibit type I deiodinases resulting in low $T_3$ and high $T_4$ levels. Amiodarone-induced hypothyroidism occurs in 5-15% of patients on amiodarone. AIH can also occur in people without pre-existing thyroid dysfunction.
- **Amiodarone-Induced thyrotoxicosis** (AIT): occurs in 2-12% of patients on amiodarone. This may be due to either an increased iodine load in patients with previously autonomous thyroid (Graves' disease, toxic multinodular goitre), or amiodarone-induced destructive thyroiditis.

**Signs and Symptoms of HYPERthyroidism**

**T**remor
**H**eart rate up
**Y**awning (fatigued)
**R**estlessness
**O**ligomenorrhea/amenorrhea
**I**ntolerance to heat
**D**iarrhea
**I**rritability
**S**weating
**M**uscle wasting/weight loss

**Common Etiologies**

| Thyrotoxicosis | Hypothyroidism |
|---|---|
| Graves' Disease | Hashimoto's |
| Toxic Nodular Goitre | Congenital |
| Toxic Nodule | Iatrogenic (thionamides, radioactive iodine, or surgery) |
| Thyroiditis | Hypothyroid phase of thyroiditis |

# Thyrotoxicosis

### Definition

- clinical, physiological, and biochemical findings in response to elevated thyroid hormone

### Epidemiology

- 1% of general population have hyperthyroidism
- F:M = 5:1

## Etiology and Pathophysiology

### Table 17. Differential Diagnosis of Thyrotoxicosis

| Disorder | TSH | Free $T_4$/$T_3$ | Thyroid Antibodies | RAIU | Other |
|---|---|---|---|---|---|
| **HYPERTHYROIDISM** | | | | | |
| **Graves' Disease** | Decreased | Increased | TRAb | Increased | Homogenous uptake on scan |
| **Toxic Nodular Goitre** | Decreased | Increased | None | Increased | Heterogeneous uptake on scan |
| **Toxic Nodule** | Decreased | Increased | None | Increased | Intense uptake in hot nodule on scan with no uptake in the rest of the gland |
| **THYROIDITIS** | | | | | |
| **Subacute, Silent, Postpartum** | Decreased | Increased | Up to 50% of cases (TSI, TPO, Tg) | Decreased (increases once entering hypothyroid phase, when TSH rises) | In classical subacute painful thyroiditis, ESR increased |
| **EXTRATHYROIDAL SOURCES OF THYROID HORMONE** | | | | | |
| **Endogenous** (struma ovariae, ovarian teratoma, metastatic follicular carcinoma) | Decreased | Increased | None | Decreased | |
| **Exogenous** (drugs) | Decreased | Increased ($T_4$ would be decreased if taking $T_3$) | None | Decreased | |
| **EXCESSIVE THYROID STIMULATION** | | | | | |
| **Pituitary Thyrotropinoma** | Increased | Increased | None | Increased | |
| **Pituitary Thyroid Hormone Receptor Resistance** | Increased | Increased | None | Increased | |
| **Increased hCG** (e.g. pregnancy) | Decreased | Increased | None | Increased<br>Test is contraindicated in pregnancy | |

## Clinical Features

### Table 18. Clinical Features of Thyrotoxicosis

| General | Fatigue, heat intolerance, irritability, fine tremor |
|---|---|
| **CVS** | Tachycardia, atrial fibrillation, palpitations<br>Elderly patients may have only cardiovascular symptoms, commonly new onset atrial fibrillation |
| **GI** | Weight loss with increased appetite, thirst, increased frequency of bowel movements (hyperdefecation) |
| **Neurology** | Proximal muscle weakness, hypokalemic periodic paralysis (more common in Asians) |
| **GU** | Oligomenorrhea, amenorrhea, decreased fertility |
| **Dermatology** | Fine hair, skin moist and warm, vitiligo, soft nails with onycholysis (Plummer's nails), palmar erythema, pruritis<br>Graves' disease: clubbing (acropachy), pretibial myxedema (rare) |
| **MSK** | Decreased bone mass, proximal muscle weakness |
| **Hematology** | Graves' disease: leukopenia, lymphocytosis, splenomegaly, lymphadenopathy (occasionally) |
| **Eye** | Graves' disease: lid lag, retraction, proptosis, diplopia, decreased acuity, puffiness, conjuctival injection<br>NOTE: Lid lag is a reflection of a hyperadrenergic state and can be present in any form of thyrotoxicosis |

## Treatment

- β-blockers for control of adrenergic symptoms
- antithyroidals (thionamides): propylthiouracil (PTU) or methimazole (MMI); MMI recommended (except in first trimester pregnancy); block thyroid hormone production
  - antithyroidals to prepare patients with endogenous hyperthyroidism for surgery, for patients with Graves' disease, and for patients with toxic nodules who do not wish to have definitive treatment with radioactive iodine or surgery
- radioactive iodine thyroid ablation for Graves' disease and toxic nodules/adenoma
- surgery in the form of hemi, subtotal, or complete thyroidectomy for toxic nodules
- surgery in the form of total or near total thyroidectomy for Graves' disease

# Graves' Disease

## Definition
- an autoimmune disorder characterized by autoantibodies that stimulate the TSH receptor leading to hyperthyroidism

## Epidemiology
- most common cause of hyperthyroidism
- occurs at any age with peak in 3rd and 4th decade
- F:M = 7:1, 1.5-2% of U.S. women
- familial predisposition: 15% of patients have a close family member with Graves' disease and 50% have family members with positive circulating antibodies
- association with HLA-B8 and DR3
- may be associated with other autoimmune disorders (e.g. pernicious anemia, Hashimoto's disease)

## Etiology and Pathophysiology
- autoimmune disorder due to breakdown in thyroid tolerance likely due to a combination of factors including autoreactive B lymphocytes and an imbalance favouring a Th2 vs Th1 immune response
- B lymphocytes produce thyroid-stimulating immunoglobulin (TSI) that binds and stimulates the TSH receptor and stimulates the thyroid gland
- immune response can be triggered by postpartum state, iodine excess, viral or bacterial infections, glucocorticoid withdrawal
- ophthalmopathy (thyroid associated orbitopathy) is a result of increased connective and extraocular muscle tissue volume due to inflammation and accumulation of glycosaminoglycans, stimulated by TSI, that increase osmotic pressure within the orbit; this leads to fluid accumulation and forward displacement of the eyeball
- dermopathy (pretibial or localized myxedema) may be related to cutaneous glycosaminoglycan deposition

## Clinical Features
- signs and symptoms of thyrotoxicosis
- diffuse goitre ± thyroid bruit secondary to increased blood flow through the gland
- ophthalmopathy: proptosis, diplopia, conjunctival injection, corneal abrasions, periorbital puffiness, lid lag, decreased visual acuity (plus signs of hyperthyroidism: lid retraction, characteristic stare)
- dermopathy (rare): pretibial myxedema: thickening of dermis that manifests as non-pitting edema
- acropachy: clubbing and thickening of distal phalanges

## Investigations
- low TSH
- increased free $T_4$ (and/or increased $T_3$)
- positive for TRAb (sensitivity and specificity of third-generation TRAb tests that are available currently is over 98 percent allowing their use for determining the etiology of hyperthyroidism)
- increased radioactive iodine (I-131) uptake
- homogeneous uptake on thyroid scan

## Treatment
- treatment for Graves' disease includes thionamides, radiodine (RAI), or surgery. These treatment options are not mutually exclusive. Patients who start with medical management, may eventually require a definitive treatment with RAI or surgery
- thionamides (antithyroid medications): propylthiouracil (PTU) or methimazole (MMI)
  - PTU and MMI inhibit thyroid hormone synthesis by inhibiting peroxidase-catalyzed reactions, thereby inhibiting organification of iodide, blocking the coupling of iodotyrosines
  - PTU also inhibits peripheral deiodination of $T_4$ to $T_3$
  - treat for approximately 12-18 mo aiming for a normal TSH and TRAb prior to consideration of treatment discontinuation
  - small goitre, mild hyperthyroidism, and low TRAb titres are good predictors for long-term remission with medical therapy
  - remission (normal thyroid indices one year after discontinuation of PTU or MMI) rates range between 20-30% following 12-18 mo of antithyroid medication
  - major side effects: hepatotoxicity (cholestasis, hepatitis), agranulocytosis, vasculitis
  - minor side effects: minor rash, pruritus
  - MMI preferred vs. PTU due to longer duration of action (once daily dosing for most), more rapid resolution of hyperthyroidism , and lower incidence of side effects
  - in pregnancy: use PTU during first 16 weeks of pregnancy and MMI after. MMI is contraindicated in the first trimester due to risk of aplasia cutis; MMI is preferred in the second and third trimester due to the potential risk of hepatotoxicity with PTU in the second and third trimesters
- symptomatic treatment with β-blockers
- thyroid ablation with radioactive I-131 if PTU or MMI trial does not produce disease remission or patient prefers definitive treatment with RAI
  - high incidence of hypothyroidism after I-131 requiring lifelong thyroid hormone replacement
  - contraindicated in pregnancy
  - may worsen ophthalmopathy
- total or near total thyroidectomy (indicated for large goitres, suspicious nodule for cancer, or if patient is intolerant to thionamides and refusing RAI ablation)
  - risks: hypoparathyroidism and vocal cord palsy

**Graves' Ophthalmopathy**

**NO SPECS** (in order of changes usually)
**N**o signs
**O**nly signs: lid lag, lid retraction
**S**oft tissue: periorbital puffiness, conjuctival injection, chemosis
**P**roptosis/exophthalmos
**E**xtraocular (diplopia)
**C**orneal abrasions (since unable to close eyes)
**S**ight loss

**Other Medications Used in the Treatment of Graves'**

**Glucocorticoids** have been useful in the treatment of severe Graves' hyperthyroidism and thyroid storm, by inhibiting the conversion of peripheral $T_4$ to $T_3$

**Lithium** is also used to treat Graves' hyperthyroidism. It acts by blocking thyroid hormone release, but its toxicity has limited its use in practice

**Caution with Thionamides**
These drugs are effective in controlling hyperthyroidism and induce permanent remission in 20-30% of patients with Graves' disease. They inhibit thyroid hormone synthesis. They are most often employed to achieve a euthyroid state before definitive treatment. Adverse effects include teratogenicity, agranulocytosis, hepatotoxicity, and ANCA-positive vasculitis

- ophthalmopathy/orbitopathy
  - smoking cessation is important
  - prevent drying of eyes and ulceration of cornea by using artificial tears during the day and lubricants at night
  - high dose prednisone or IV methylprednisolone in severe cases
  - high dose glucocorticoids preferably IV as well as potential orbital decompression surgery for sight threatening orbitopathy
  - orbital radiation, surgical decompression

### Prognosis
- course involves remission and exacerbation unless gland is destroyed by radioactive iodine or surgery
- total and subtotal thyroidectomy are rapid cures with low risk of recurrence (2% and 10%, respectively); risks include permanent hypothyroid and potential of damage to laryngeal nerve
- radioactive iodine is less invasive than surgery, but also results in permanent hypothyroid and requires precautions in contacts several days after treatment
- medical therapy with thionamides is not invasive, but has high recurrence rate at ~50%
- lifetime follow-up needed

## Subacute Thyroiditis (Thyrotoxic Phase)

- there are two main types: painful (DeQuervain's) and painless (silent)

**Table 19. Subacute Thyroiditis Painful versus Painless**

| | Painful Thyroiditis (DeQuervain's, granulomatous) | Painless Thyroiditis (Silent, autoimmune) |
|---|---|---|
| **Pathophysiology** | Presumed to be caused by viral infection or postviral inflammatory process<br>Strongly associated with HLA-D35<br>Thyroid inflammation damages thyroid folllicles, resulting in releasse of large amounts of T4 and T3 until stores are exhausted<br>State of hypothyroidism often persists until thyroid can generate sufficient thyroid hormones. | Considered variant of Hashimoto's thyroiditis<br>Associated with HLA-DR3<br>Postpartum subtype occurs following pregnancy<br>Also caused by inflammatory damage leading to unregulated release of T4 and 4 into circulation |
| **Clinical Features** | Painful swelling of the thyroid (may radiate to jaw and ears), transient vocal cord paresis, malaisse, fatigue, myalgia, fever<br>Often preceded by URTI<br>Painful condition lasts for a week to few months<br>Signs of hyperthyroidism during hyperthyroid phase (palpitations, tachycardia, stare) | thyroid enlargement without discomfort<br>5-20% of patients have sequence of hyperthyroidism, hypothyroidism and recovery<br>Signs of hyperthyroidism during hyperthyroid phase (palpitations, tachycardia, stare)<br>Affects women more than men |
| **Laboratory Investigations** | Initial elevated $T_4$ and $T_3$<br>Near absent RAIU<br>ESR and CRP often elevated | Initial elevated $T_4$ and $T_3$<br>Near absent RAIU |
| **Treatment** | NSAID/prednisone for pain<br>β-adrenergic blockage is usually effective in reversing most of the hypermetabolic and cardiac symptoms<br>If symptomatically hypothyoid, may treat short-term with thyroxine | β-adrenergic blockage is usually effective in reversing most of the hypermetabolic and cardiac symptoms<br>If symptomatically hypothyoid, may treat short-term with thyroxine |
| **Prognosis** | Complete spontaneous recovery to normal thyroid function in 90% of patients<br>10% of patients may become hypothyroid and require permanent replacement | 20-30% of patients may become hypothyroid and require permanent replacement<br>At risk of recurrent episodes of thyroiditis |

## Toxic Adenoma/Toxic Multinodular Goitre

### Etiology and Pathophysiology
- autonomous thyroid hormone production from a functioning adenoma that is hypersecreting $T_3$ and $T_4$
- may be singular (toxic adenoma) or multiple (toxic multinodular goitre [Plummer's disease])

### Clinical Features
- multinodular goitre
- tachycardia, heart failure, arrhythmia, weight loss, nervousness, weakness, tremor, and sweats
- seen most frequently in elderly people as opposed to Graves' disease which is more common in younger individuals

### Investigations
- low TSH, high $T_3$ and $T_4$
- thyroid scan with increased RAIU in nodule(s) and suppression of the remainder of the gland

### Treatment
- use high dose radioactive iodine (I-131) to ablate hyperfunctioning nodules
- β-blockers often necessary for symptomatic treatment prior to definitive therapy
- surgical excision may also be used as 1st line treatment

- initiate therapy with PTU or MMI to attain euthyroid state in individuals who do not wish to have definitive treatment of their disease, in preparation for thyroidectomy, and prior to RAI in patients at risk for complications due to exacerbation of hyperthyroidism following RAI such as the elderly with cardiovascular disease

# Thyrotoxic Crisis/Thyroid Storm

### Definition
- medical emergency – acute exacerbation of all of the symptoms of thyrotoxicosis presenting in a life-threatening state secondary to uncontrolled hyperthyroidism!
- rare, but serious with mortality rate between 10-30%

### Etiology and Pathophysiology
- often precipitated by infection, trauma, or surgery in a hyperthyroid patient

### Differential Diagnosis
- sepsis, pheochromocytoma, malignant hyperthermia, drug overdose, neuroleptic malignant syndrome

### Clinical Features
- hyperthyroidism
- extreme hyperthermia (≥40°C), tachycardia, vomiting, diarrhea, hepatic failure with jaundice, atrial fibrillation, congestive heart failure
- central nervous system manifestations including agitation, delirium, psychosis, lethargy, seizures, coma

### Laboratory Investigations
- increased free $T_3$ and $T_4$, undetectable TSH
- ± anemia, leukocytosis, hyperglycemia, hypercalcemia, elevated LFTs

### General Measures
- fluids, electrolytes, and vasopressor agents should be used as indicated
- a cooling blanket and acetaminophen can be used to treat the pyrexia
- propranolol or other β-blockers that additionally decrease peripheral conversion of $T_4 \rightarrow T_3$ can be used, but should be used with caution in patients with decompensated heart failure as it may worsen condition

### Specific Measures
- PTU is the anti-thyroid drug of choice and is used in high doses (200 mg q4h)
- give iodide, which acutely inhibits the release of thyroid hormone, 1 h after the first dose of PTU is given
  - Sodium iodide 1 g IV drip over 12 h q12h
    OR
  - Lugol's solution 10 drops q8h
    OR
  - Potassium iodide (SSKI) 5 drops q6h
- hydrocortisone 100 mg IV q8h or dexamethasone 2-4 mg IV q6h for the first 24-48 h; inhibits peripheral conversion of $T_4 \rightarrow T_3$

# Hypothyroidism

### Definition
- clinical syndrome caused by cellular responses to insufficient thyroid hormone production

### Epidemiology
- 2-3% of general population
- F:M = 10:1
- 10-20% of women >50 have subclinical hypothyroidism (normal $T_4$, TSH mildly elevated)
- iodine deficiency most common cause worldwide, but not in North America

### Etiology and Pathophysiology
- primary hypothyroidism (90%)
  - inadequate thyroid hormone production secondary to intrinsic thyroid defect
  - iatrogenic: post-ablative (I-131 or surgical thyroidectomy)
  - autoimmune: Hashimoto's thyroiditis
  - hypothyroid phase of subacute thyroiditis
  - drugs: goitrogens (iodine), PTU, MMI, lithium
  - infiltrative disease (progressive systemic sclerosis, amyloid)
  - iodine deficiency
  - congenital (1/4000 births)
  - neoplasia



**Factors Affecting Gastrointestinal Absorption of Levothyroxine: A Review**
Clin Ther 2017;39(2):378-403
- GI disorders such as celiac disease, atrophic gastritis, lactose intolerance, *H. pylori* infection may impede levothyroxine absorption.
- Drugs decreasing stomach acidity have been shown to significantly reduce exogenous thyroid hormone absorption from the GI tract. These include: proton-pump inhibitors, H2 receptor antagonists, calcium carbonate, sucralfate and aluminum hydroxide.
- Iron citrate is shown to reduce intestinal absorption of levothyroxine.
- Food, especially soybeans and coffee, have been shown to reduce absorption of levothyroxine significantly.
- Roughly 80% of levothyroxine is absorbed within 3 h after administration of the drug. Thus, patients should be educated to take levothyroxine on empty stomach at least one hour prior to eating breakfast.

- secondary hypothyroidism: pituitary hypothyroidism
  - insufficiency of pituitary TSH
- tertiary hypothyroidism: hypothalamic hypothyroidism
  - decreased TRH from hypothalamus (rare)
- peripheral tissue resistance to thyroid hormone (Refetoff syndrome)

**Table 20. Interpretation of Serum TSH and Free T4 in Hypothyroidism**

| | Serum TSH | Free $T_4$ |
|---|---|---|
| **Overt Primary Hypothyroidism** | Increased | Decreased |
| **Subclinical Primary Hypothyroidism** | Increased | Normal |
| **Secondary Hypothyroidism** | Decreased or not appropriately elevated | Decreased |

### Clinical Features

**Table 21. Clinical Features of Hypothyroidism**

| | |
|---|---|
| **General** | Fatigue, cold intolerance, slowing of mental and physical performance, hoarseness, macroglossia |
| **CVS** | Pericardial effusion, bradycardia, hypotension, worsening CHF + angina, hypercholesterolemia, hyperhomocysteinemia, myxedema heart |
| **Respiratory** | Decreased exercise capacity, hypoventilation secondary to weak muscles, decreased pulmonary responses to hypoxia, sleep apnea due to macroglossia |
| **GI** | Weight gain despite poor appetite, constipation |
| **Neurology** | Paresthesia, slow speech, muscle cramps, delay in relaxation phase of deep tendon reflexes ("hung reflexes"), carpal tunnel syndrome, asymptomatic increase in CK, seizures |
| **GU** | Menorrhagia, amenorrhea, impotence |
| **Dermatology** | Puffiness of face, periorbital edema, cool and pale, dry and rough skin, hair dry and coarse, eyebrows thinned (lateral 1/3), discolouration (carotenemia) |
| **Hematology** | Anemia: 10% pernicious due to presence of anti-parietal cell antibodies with Hashimoto's thyroiditis |

### Treatment
- L-thyroxine (dose range: 0.05-0.2 mg PO OD ~1.6 µg/kg/d)
- elderly patients and those with CAD: start at 0.025 mg daily and increase gradually every 6 wk (start low, go slow)
- after initiating L-thyroxine, TSH needs to be evaluated in 6 wk; dose is adjusted until TSH returns to normal reference range
- once maintenance dose achieved, follow-up TSH with patient annually
- secondary/tertiary hypothyroidism
  monitor via measurement of free $T_4$ (TSH is unreliable in this setting)

### CONGENITAL HYPOTHYROIDISM
- see Pediatrics, P29

## Hashimoto's Thyroiditis

### Definition
- most common form of primary hypothyroidism in North America
- chronic autoimmune thyroiditis characterized by both cellular and humoral factors in the destruction of thyroid tissue
- two major forms: goitrous and atrophic; both forms share same pathophysiology but differ in the extent of lymphocytic infiltration, fibrosis, and thyroid follicular cell hyperplasia
- goitrous variant usually presents with a small, rubbery goitre and euthyroidism, then hypothyroidism becomes evident
  - associated with fibrosis
- atrophic variant patients are hypothyroid from the start associated with thyroid lymphoma

### Etiology and Pathophysiology
- defect in clone of T-suppressors leads to cell-mediated destruction of thyroid follicles
- B lymphocytes produce antibodies against thyroid components including thyroglobulin, thyroid peroxidase, TSH receptor, $Na^+/I^-$ symporter

### Risk Factors
- F:M = 7:1
- genetic susceptibility: increased frequency in patients with Down's syndrome, Turner's syndrome, certain HLA alleles, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)
- family Hx or personal Hx of other autoimmune diseases
- cigarette smoking
- high iodine intake

### Investigations
- high TSH, low $T_4$ (not necessary to measure $T_3$ as it will be low as well)
- presence of anti-thyroid peroxidase (TPOAb) and thyroglobulin antibodies (TgAb) in serum

### Treatment
- if hypothyroid, replace with L-thyroxine (analog of $T_4$)

**Thyroid Hormone Replacement for Subclinical Hypothyroidism**
Cochrane DB Syst Rev 2007;3:CD003419
**Purpose:** To assess the effects of thyroid hormone replacement for subclinical hypothyroidism.
**Study Selection:** RCTs comparing thyroid hormone replacement with placebo in adults with subclinical hypothyroidism. Minimum duration of follow-up was 1 mo.
**Results:** No trial assessed (cardiovascular) mortality or morbidity. Seven studies evaluated symptoms, mood, and quality of life with no statistically significant improvement. One study showed a statistically significant improvement in cognitive function. Six studies assessed serum lipids; there was a trend for reduction in some parameters following levothyroxine replacement. Some echocardiographic parameters improved after levothyroxine replacement therapy, like myocardial relaxation. Only four studies reported adverse events with no statistically significant differences between groups.
**Conclusions:** In current RCTs, levothyroxine replacement therapy for subclinical hypothyroidism did not result in improved survival or decreased cardiovascular morbidity. Data on health-related quality of life and symptoms did not demonstrate significant differences between intervention groups. Some evidence indicates that levothyroxine replacement improves some parameters of lipid profiles and left ventricular function.

**Signs and Symptoms of Hypothyroidism**

**HIS FIRM CAP**
**H**ypoventilation
**I**ntolerance to cold
**S**low HR
**F**atigue
**I**mpotence
**R**enal impairment
**M**enorrhagia/amenorrhea
**C**onstipation
**A**nemia
**P**aresthesia

# Myxedema Coma

### Definition
- medical emergency – severe hypothyroidism complicated by trauma, sepsis, cold exposure, MI, inadvertent administration of hypnotics or narcotics, and other stressful events
- rare; high level of mortality (up to 40%, despite therapy)

### Clinical Features
- hallmark symptoms of decreased mental status and hypothermia
- hyponatremia, hypotension, hypoglycemia, bradycardia, hypoventilation, and generalized non-pitting edema often present

### Investigations
- decreased $T_4$, increased TSH, decreased glucose
- check ACTH and cortisol for evidence of adrenal insufficiency

### Treatment
- aggressive and immediate treatment required
- ABCs: ICU admission
- corticosteroids (for risk of concomitant adrenal insufficiency): hydrocortisone 100 mg q8h
- L-thyroxine 0.2-0.5 mg IV loading dose, then 0.1 mg IV OD until oral therapy tolerated; also consider $T_3$ therapy
- supportive measures: mechanical ventilation, vasopressor drugs, passive rewarming, IV dextrose, fluids if necessary (risk of overload)
- monitor for arrhythmia

# Sick Euthyroid Syndrome

### Definition
- changes in the regulation of the hypothalamic-pituitary-thyroid axis and thyroid hormone metabolism and transport amongst patients with severe illness, trauma, surgery, or starvation
- not due to intrinsic thyroid,pituitary, or hypothalamic disease
- initially low free $T_3$ may be followed by low TSH and if severe illness low free $T_4$
- with recovery of illness, TSH may become transiently high

### Pathophysiology
- abnormalities include alterations in:
  - peripheral transport and metabolism of thyroid hormone
  - regulation of TSH secretion
- may be protective during illness by reducing tissue catabolism

### Labs
- initially decreased free $T_3$ followed by decreased TSH and finally decreased free $T_4$

### Treatment
- treat the underlying disease; thyroid hormone replacement has not shown to be beneficial
- thyroid function tests normalize once patient is well (initially with a transient increase in TSH)

# Non-Toxic Goitre

### Definition
- generalized enlargement of the thyroid gland in a euthyroid individual that does not result from inflammatory or neoplastic processes

### Pathophysiology
- the appearance of a goitre is more likely to present during adolescence, pregnancy, and lactation due to increased thyroid hormone requirements
  - early stages: goitre is usually diffuse
  - later stages: multinodular non-toxic goitre with nodule, cyst formation and areas of ischemia, hemorrhage, and fibrosis

### Etiology
- iodine deficiency or excess
- rogens: brassica vegetables (e.g. turnip, cassava)
- drugs: iodine, lithium, para-aminosalicylic acid
- any disorder of hormone synthesis with compensatory growth
- peripheral resistance to thyroid hormone

### Treatment
- remove goitrogens
- radioiodine therapy (need very high doses given low iodine uptake, used as last resort)
- suppression with L-thyroxine (rarely done)
- surgery may be necessary for severe compressive symptoms; however, these patients are often asymptomatic

### Complications
- compression of neck structures causing stridor, dysphagia, pain, and hoarseness of voice
- multinodular goitre may become autonomous leading to toxic multinodular goitre and hyperthyroidism

## Thyroid Nodules

### Definition
- discrete lesion that and be distinguished sonographicallyfrom the rest of the thyroid parenchyma
- nodules found incidentally on ultrasound suggests a prevalence of 19-67%

### Etiology
- benign tumours (e.g. follicular adenoma)
- thyroid malignancy
- hyperplastic area in a multinodular goitre
- cyst: true thyroid cyst, area of cystic degeneration in a multinodular goitre

### Investigations

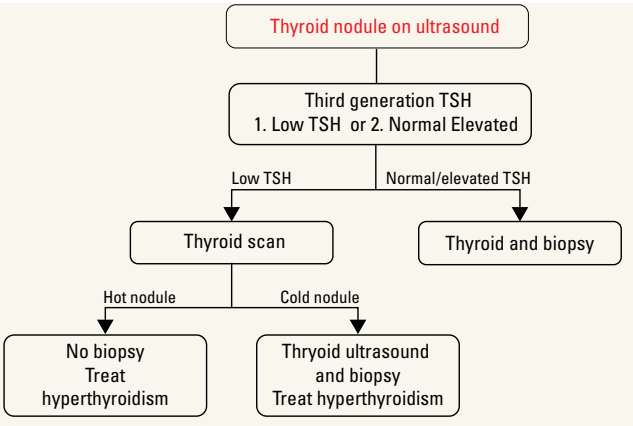



**Figure 10. Approach to the evaluation of a thyroid nodule**
Adapted from Dr. J Goguen, University of Toronto, MMMD 2013

## Thyroid Malignancies

- see Otolaryngology, OT37

# Adrenal Cortex

## Adrenocorticotropic Hormone

- a polypeptide (cleaved from prohormone POMC), secreted in a pulsatile fashion from the anterior pituitary with diurnal variability (peak: 0200-0400 h; trough: 1800-2400 h)
- secretion regulated by corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP)
- stimulates growth of adrenal cortex and release of glucocorticoids, androgens and, to a very limited extent, mineralocorticoids
- ACTH can directly bind to MSH receptors on melanocytes, enhancing melanogenesis

## Adrenocortical Hormones

### Aldosterone
- a mineralocorticoid which regulates extracellular fluid (ECF) volume through $Na^+$ (and $Cl^-$) retention and $K^+$ (and $H^+$) excretion (stimulates distal tubule $Na^+/K^+$ ATPase)
- regulated by the renin-angiotensin-aldosterone system and by hyperkalemia
- negative feedback to juxtaglomerular apparatus (JGA) by long loop (aldosterone ↑ volume expansion) and short loop (angiotensin II ↑ peripheral vasoconstriction)

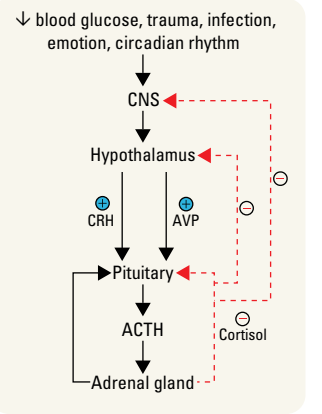



**Figure 11. Regulation of CRH-ACTH-adrenal gland axis**

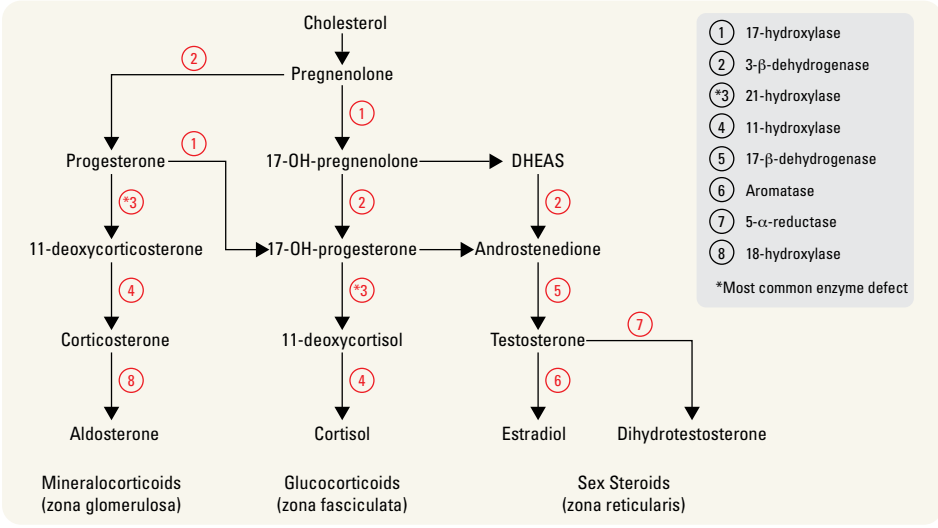



**Figure 12. Pathways of major steroid synthesis in the adrenal gland and their enzymes**

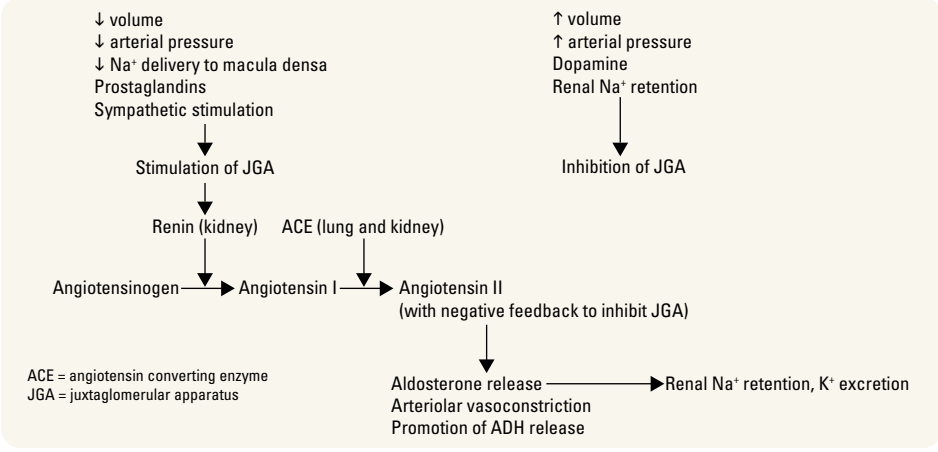



**Figure 13. Renin-angiotensin-aldosterone axis (see Nephrology, NP4)**

**Layers of the Adrenal Cortex**

**OUTSIDE**

**Zona Glomerulosa** produces **mineralocorticoids (aldosterone)**

**Zona Fasciculata** produces **glucocorticoids (cortisol)**

**Zona Reticularis** produces **androgens (DHEA, androstenedione)**

**INSIDE**

## Cortisol

- a glucocorticoid, regulated by the HPA axis
- involved in the regulation of metabolism
- supports blood pressure and vasomotor tone
- also involved in behavioural regulation and immunosuppression

**Table 22. Physiological Effects of Glucocorticoids**

| Stimulatory Effects | Inhibitory Effects |
|---|---|
| Stimulate hepatic glucose production (gluconeogenesis) | Inhibit bone formation; stimulate bone resorption |
| Increase insulin resistance in peripheral tissues | Inhibit fibroblasts, causing collagen and connective tissue loss |
| Increase protein catabolism | Suppress inflammation; impair cell-mediated immunity |
| Stimulate leukocytosis and lymphopenia | Inhibit growth hormone axis* |
| Increase cardiac output, vascular tone, $Na^+$ retention | Inhibit reproductive axis* |
| Increase PTH release, urine calcium excretion | Inhibit vitamin D3 and inhibit calcium uptake |

*Typically only occurs with cortisol excess

## Androgens

- sex steroids regulated by ACTH; primarily responsible for adrenarche (growth of axillary and pubic hair)
- principal adrenal androgens are: dihydroepiandrosterone (DHEA), androstenedione, and 11-hydroxyandrostenedione
- proportion of total androgens (adrenal to gonadal) increases in old age

# Adrenocortical Functional Workup

### STIMULATION TEST
- purpose: diagnosis of hormone deficiencies
- method: measure target hormone after stimulation with tropic (pituitary) hormone

### Tests of Glucocorticoid Reserve
- Cosyntropin (ACTH analogue) Stimulation Test
  - administer 250 µg cosyntropin IV/IM, and measure plasma cortisol levels before and 30 and 60 min after administration
  - physiologic response: stimulated plasma cortisol of >1500 nmol/L (>18 µg/L) at 30 or 60 min
  - inappropriate response: inability to stimulate increased plasma cortisol
- insulin tolerance test is the gold standard test used to diagnose adrenal insufficiency (see *Pituitary Gland*, E16)

### SUPPRESSION TESTS
- purpose: diagnosis of hormone hypersecretion
- method: measure target hormone after suppression of its tropic (pituitary) hormone

### 1. Tests of Pituitary-Adrenal Suppressibility
- Dexamethasone (DXM) Suppression Test
  - principle: DXM suppresses pituitary ACTH, plasma cortisol should be lowered if HPA axis is normal
  - *Screening Test*: Overnight DXM Suppression Test
    - oral administration of 1 mg DXM at midnight, then measure plasma cortisol levels the following day at 8 AM
    - physiologic response: plasma cortisol <50 nmol (<1.8 µg/dL)
    - inappropriate response: failure to suppress plasma cortisol
    - false positive results due to obesity, depression, alcoholism, medications inducing the metabolism of dexamethasone
  - *Confirmatory Test*: other testing is used to confirm the diagnosis, such as:
    - 24 h urine free cortisol (shows overproduction of cortisol)
    - midnight salivary cortisol (if available), shows lack of diurnal variation
      - inappropriate response: remains high (normally will be low at midnight)

### 2. Tests of Mineralocorticoid Suppressibility
- multiple medications interfere with the interpretation of screening and confirmatory tests for primary aldosteronism and these may need to be held prior to testing
- positive screen test for primary aldosteronism is elevated aldosterone:renin ratio in the presence of a low renin and high aldosteroneand an andosterone ≥416 pmol/L
- confirmation of primary aldosteronism requires lack of aldosterone suppression: with expansion of extracellular fluid volume (ECFV), plasma aldosterone should be lowered
- ECFV Expansion with Normal Saline (NS)
  - IV infusion of 500 mL/h of NS for 4 h, then measure plasma aldosterone levels
  - plasma aldosterone >277 pmol/L is consistent with primary hyperaldosteronsim, <140 pmol/L is normal
  - inappropriate response: failure to suppress plasma aldosterone

# Mineralocorticoid Excess Syndromes

### Definition
- primary aldosteronism (PA): excess aldosterone production (intra-adrenal cause) (previously called hyperaldosteronism)
- secondary aldosteronism (SA): aldosterone production in response to excess RAAS (extra-adrenal cause)

### Etiology
- primary hyperaldosteronism
  - aldosterone-producing adrenal adenoma (Conn's syndrome)
  - bilateral or idiopathic adrenal hyperplasia
  - glucocorticoid-remediable aldosteronism
  - aldosterone-producing adrenocortical carcinoma
  - unilateral adrenal hyperplasia
  - ectopic aldosterone-producing tumours
  - familial hyperaldosteronism (FH) types I-IV
- secondary hyperaldosteronism

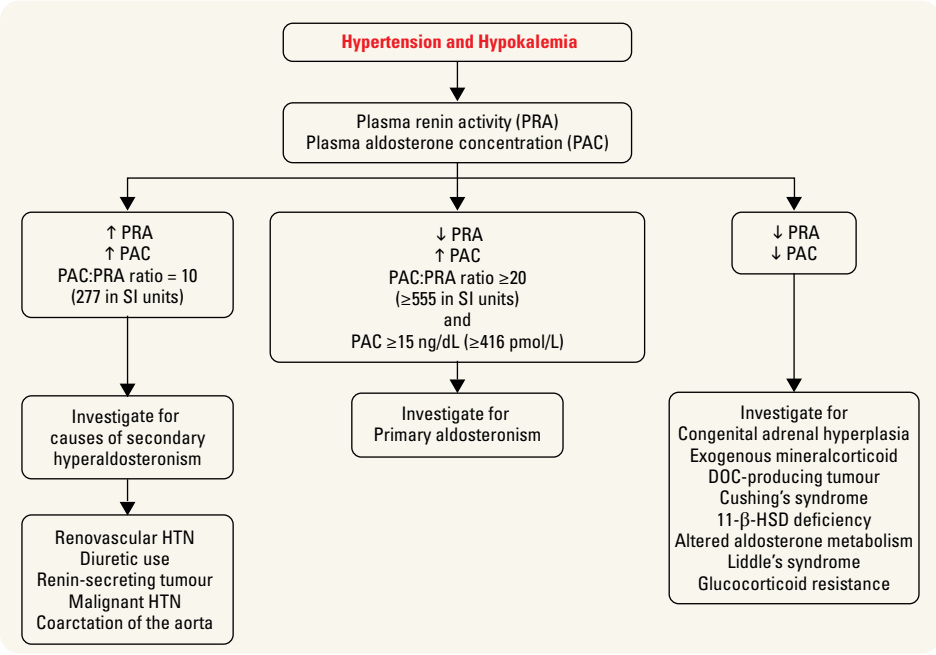



**Figure 14. Approach to mineralocorticoid excess syndromes**

## Clinical Features

- HTN
- hypokalemia (± mild hypernatremia), metabolic alkalosis
- normal $K^+$, hyponatremia in SH (low effective circulating volume leads to ADH release)
- increased cardiovascular risk: LV hypertrophy, atrial fibrillation, stroke, and MI
- elevated risk of metabolic syndrome and T2DM
- fatigue, weakness, paresthesia, headache; severe cases present with tetany, intermittent paralysis (only if $K^+$ <2.5 mEq/L)

## Diagnosis

- investigate plasma aldosterone:renin ratio in patients with HTN and hypokalemia, drug resistant HTN, HTN and a first degree relative with primary aldosteronism, HTN and a family history of stoke in a first degree relative 40 yr, HTN and adrenal incidentaloma
- confirmatory testing for PA: aldosterone suppression test (demonstrate inappropriate aldosterone secretion with ECF volume expansion), adrenal vein sampling may be required to determine whether there is lateralization of aldosterone excess
- imaging: CT adrenal glands

**Table 23. Diagnostic Tests in Hyperaldosteronism**

| Test | Primary Hyperaldosteronism | Secondary Hyperaldosteronism |
|---|---|---|
| **Plasma aldosterone to renin ratio (PAC/PRA)** | Elevated (↑ aldo, ↓ renin) | Normal (↑ aldo, ↑ renin) |
| **Salt loading test (confirmatory test)** | ↑ urine aldosterone | Not performed |
| **A) Oral test** | ↑ plasma aldosterone | |
| **B) IV saline test** | plasma aldosterone concentration >277 pmol/L (140-277 indeterminant range) | |

## Treatment

- inhibit action of aldosterone: spironolactone, eplerenone, triamterene, amiloride (act on sodium channels)
- surgical excision of adrenal adenoma
- secondary hyperaldosteronism: treat underlying cause

# Cushing's Syndrome

### Definition
- results from chronic glucocorticoid excess (endogenous or exogenous sources)

### Etiology
- ACTH-dependent (85%) – bilateral adrenal hyperplasia and cortisol hypersecretion due to:
  - ACTH-secreting pituitary adenoma (Cushing's disease; 80% of ACTH-dependent)
  - ectopic ACTH-secreting tumour (e.g. small cell lung carcinoma, bronchial, carcinoid, pancreatic islet cell, pheochromocytoma, or medullary thyroid tumours)
- ACTH-independent (15%)
  - primary adrenocortical tumours: adenoma and carcinoma (uncommon)
  - bilateral adrenal nodular hyperplasia
- iatrogenic CS is probably more common than endogenous cortisol excess but is not frequently reported, it is of course ACTH-independent

### Clinical Features
- symptoms: weakness, insomnia, mood disorders, impaired cognition, easy bruising, oligo-/amenorrhea, hirsutism, and acne (ACTH dependent)
- signs: central obesity, round face ("moon face"), supraclavicular and dorsal fat pads, facial plethora, proximal muscle wasting, purple abdominal striae, skin atrophy, acanthosis nigricans, HTN, hyperglycemia, osteoporosis, pathologic fractures, hyperpigmentation, hyperandrogenism (if ACTH-dependent)

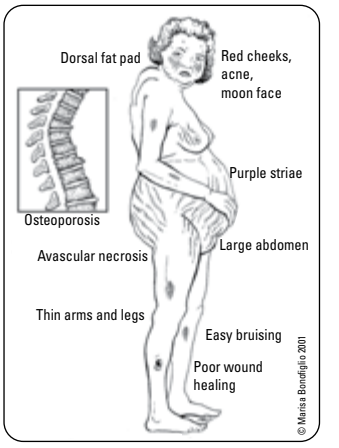


**Figure 15. Clinical features of Cushing's syndrome**

### Diagnosis
- complete a drug history to exclude exogenous sources for Cushing's syndrome
- perform one of: 1) 24 h urine free cortisol (x2 samples), 2) low dose dexamethasone suppression test, or 3) late night salivary cortisol
- consider reasons for a false positive (e.g. pregnancy, depression, alcoholism, morbid obesity, poorly controlled DM)
- confirm with one of the remaining tests

### Treatment
- adrenal
  - adenoma: unilateral adrenalectomy (curative) with glucocorticoid supplementation post-operatively, tapering slowly until HPA axis has recovered
  - carcinoma: adrenalectomy in patients with disease localized to the adrenal, adjunctive mitotane for individuals with high risk for current disease. Mitotane ± chemotherapy for patients with metastatic disease
  - medical treatment: ketoconazole to reduce cortisol, mitotane can be used – typically reserved for patients with malignant disease
- pituitary
  - transsphenoidal resection, with glucocorticoid supplementation post-operatively
  - if surgery delayed, contraindicated, or unsuccessful, consider medical management e.g. adrenal enzyme inhibitors (such as ketoconazole, metyrapone, and etomidate), glucocorticoid receptor antagonist (such as mifepristone)
- ectopic ACTH tumour (paraneoplastic syndrome): usually bronchogenic cancer (poor prognosis) surgical resection, if possible; chemotherapy/radiation for primary tumour
  - medical treatment with mitotane or ketoconazole to reduce cortisol synthesis. Often required when surgery is delayed, contraindicated, or unsuccessful

# Congenital Adrenal Hyperplasia

- see Pediatrics, P31

# Hyperandrogenism

## Definition
- state of having excessive secretion of androgens (DHEA, DHEA-sulfate, testosterone)

## Etiology and Pathophysiology

**Table 24. Etiology of Hyperandrogenism**

| | |
|---|---|
| **Medications Androgen-Mediated** | Anabolic steroids, ACTH, androgens, progestational agents |
| **Ovarian** | PCOS<br>Ovarian hyperthecosis<br>Theca cell tumours<br>Pregnancy: placental sulfatase/aromatase deficiency |
| **Adrenal** | Congenital adrenal hyperplasia (CAH, late-onset CAH)<br>Tumours (adenoma, carcinoma) |
| **Pituitary** | Cushing's disease – high ACTH<br>Hyperprolactinemia |

## Clinical Features

### Females
- hirsutism
  - male pattern growth of androgen-dependent terminal body hair in women: back, chest, upper abdomen, face, linea alba
  - Ferriman-Gallwey scoring system is used to quantify severity of hirsutism (score of >8 is abnormal for white/black women, >9 abnormal for Mediterranean/Hispanic/Middle-Eastern women, >2 for Asian women)
- virilization
  - frontal balding, clitoromegaly, increased muscle mass, deepening of the voice
- amenorrhea, ↓ breast size, infertility

**Conditions that do Not Represent True Hirsutism**
- Androgen-independent hair (e.g. lanugo hair)
- Drug-induced hypertrichosis (e.g. phenytoin, diazoxide, cyclosporine, minoxidil)
- Topical steroid use

### Males
- minimal effects on hair, muscle mass, etc.
- inhibition of gonadotropin secretion may cause reduction in: testicular size, testicular testosterone production, and spermatogenesis

## Investigations
- testosterone, DHEA-S as a measure of adrenal androgen production
- LH/FSH (commonly in PCOS >2.5)
- 17-OH progesterone, elevated in CAH due to 21-OH deficiency; check on day 3 of menstrual cycle with a progesterone level
- for virilization: CT/MRI of adrenals and ovaries (identify tumours)
- if PCOS, check blood glucose, lipids

## Treatment
- discontinue causative medications
- antiandrogens, e.g. spironolactone
- oral contraceptives (increase sex hormone binding globulin, which binds androgens>estrogens; reduces ovarian production of androgens)
- surgical resection of tumour
- glucocorticoid ± mineralocorticoid if CAH confirmed
- treat specific causative disorders, e.g. tumours, Cushing's, etc.
- cosmetic therapy (laser, electrolysis)

# Adrenocortical Insufficiency

## Definition

- state of inadequate cortisol and/or aldosterone production by the adrenal glands

## Etiology

### PRIMARY (ADDISON'S DISEASE)

**Table 25. Etiology of Primary Adrenocortical Insufficiency**

| | |
|---|---|
| **Autoimmune (70-90%)** | Isolated adrenal insufficiency<br>Polyglandular autoimmune syndromes types I and II<br>Antibodies often directed against adrenal enzymes and 3 cortical zones |
| **Infections** | Tuberculosis (7-20%) (most common in developing world)<br>Fungal: histoplasmosis, paracoccidioidomycosis<br>HIV, CMV<br>Syphilis<br>African trypanosomiasis |
| **Infiltrative** | Metastatic cancer (lung>stomach>esophagus>colon>breast); lymphoma<br>Sarcoidosis, amyloidosis, hemochromatosis |
| **Vascular** | Bilateral adrenal hemorrhage (risk increased by heparin and warfarin)<br>Sepsis (meningococcal, *Pseudomonas*)<br>Coagulopathy in adults or Waterhouse-Friderichsen syndrome in children<br>Thrombosis, embolism, adrenal infarction |
| **Drugs** | Inhibit cortisol: ketoconazole, etomidate, megestrol acetate<br>Increase cortisol metabolism: rifampin, phenytoin, barbiturates |
| **Others** | Adrenoleukodystrophy and adrenomyeloneuropathy<br>Congenital adrenal hypoplasia (impaired steroidogenesis)<br>Familial glucocorticoid deficiency or resistance<br>Defective cholesterol metabolism |

### SECONDARY ADRENOCORTICAL INSUFFICIENCY

- inadequate pituitary ACTH secretion
- multiple etiologies (see *Hypopituitarism*, E20), including withdrawal of exogenous steroids

## Clinical Features

**Table 26. Clinical Features of Primary and Secondary Adrenal Insufficiency (AI)**

| | Primary AI (Addison's or Acute AI) | Secondary AI |
|---|---|---|
| **Skin and Mucosa** | Dark (palmar crease, extensor surface) | Pale |
| **Potassium** | High | Normal |
| **Sodium** | Normal or Low | Normal or Low |
| **Metabolic Acidosis** | Present | Absent |
| **Associated Diseases** | Primary hypothyroidism, T1DM, vitiligo | Central hypogonadism or hypothyroidism, growth hormone deficiency, DI |
| **Associated Symptoms** | Weakness, fatigue, weight loss, hypotension, salt craving, postural dizziness, myalgia, arthralgia<br>GI: N/V, abdominal pain, diarrhea | Weakness, fatigue, weight loss, hypotension, postural dizziness, myalgia, arthralgia, headaches, visual abnormalities |
| **Diagnostic Test** | Cosyntropin Stimulation Test<br>High morning plasma ACTH<br>High renin | Insulin tolerance test<br>Cosyntropin Stimulation Test<br>Low or inappropriately low morning plasma ACTH |

Adapted from: Salvatori R. JAMA 2005;294:2481-2488

## Treatment

- acute adrenal crisis – can be life-threatening
  - IV NS 1L within the first hour followed by continuous IV NS guided by patient requirements; add D5W if hypoglycemic
  - hydrocortisone 100 mg IV stat followed by 50 mg IV q6h
  - identify and correct precipitating factors
- maintenance
  - hydrocortisone 15-25 mg total daily dose, in 2-3 divided doses, highest dose in the AM
  - Florinef™ (fludrocortisone, synthetic mineralocorticoid) 0.05-0.2 mg PO daily if mineralocorticoid deficient, increase dose of steroids 2-3 fold for a few days during moderate-severe illness (e.g. with vomiting, fever)
  - major stress (e.g. surgery, trauma) requires 150-300 mg hydrocortisone IV daily divided into 3 doses
  - medical alert bracelet and instructions for emergency hydrocortisone/dexamethasone IM/SC injection

# Adrenal Medulla

## Catecholamine Metabolism

- catecholamines are synthesized from tyrosine in postganglionic sympathetic nerves (norepinephrine) and chromaffin cells of adrenal medulla (epinephrine)
- broken down into metanephrines and other metabolites (VMA, HVA) and excreted in urine



**ABC of Adrenaline**

**A**drenaline activates
**β**-receptors, increasing
**C**yclic AMP

## Pheochromocytoma/Paraganglioma

### Definition

- paragangliomas are rare neuroendocrine tumours that arise from the extra-adrenal autonomic paraganglia (small organs comprised of neuroendocrine cells that secrete catecholamines)
- pheochromocytomas are catecholamine-secreting tumours derived from chromaffin cells of the adrenal gland

### Epidemiology

- most commonly a single tumour of adrenal medulla
- rare cause of HTN (<0.2% of all hypertensives)

### Etiology and Pathophysiology

- pheochromocytomas and paragangliomas are the most inherited among neuroendocrine tumours
- 30-40% cases are linked to germline mutations, including mutations in the RET, VHL, SDHx, NF1, and SDHAF2 genes
- pheochromocytomas and paragangliomas are divided into clusters: Cluster 1 - Pseudohypoxia subtype (FH, VHL/EPAS1-related), Cluster 2- Kinase signaling group (HRAS), Cluster 3 - WNT signaling group (CSDE1, UBTF-MAML3 fusion)
- most cases sporadic, 40% patients have the disease as part of a familial disorder and in these patients, the tumours are more likely to be bilateral adrenal pheochromocytoma/paragangliomas
- hereditary forms present earlier than sporadic cases
- several familial disorders are associated with adrenal pheochromocytoma, all have autosomal dominant inheritance, e.g. multiple endocrine neoplasia type 2 (MEN2) - 50% frequency, von Hippel-Lindau (VHL) syndrome - 10-20% frequency, and less commonly, neurofibromatosis type 1 (NF1) - 0.1-5.7%
- tumours, via unknown mechanism, able to synthesize and release excessive catecholamines

### Clinical Features

- 50% suffer from paroxysmal HTN; the rest have sustained HTN
- classic triad (not found in most patients): episodic "pounding" headache, palpitations/tachycardia, diaphoresis
- other symptoms: tremor, anxiety, chest or abdominal pain, nausea and vomiting, visual blurring, weight loss, polyuria, polydipsia
- other signs: orthostatic hypotension, papilledema, hyperglycemia, dilated cardiomyopathy
- symptoms may be triggered by stress, exertion, anesthesia, abdominal pressure, certain foods (especially tyramine containing foods – such as aged/strong cheese and cured meats)

### Investigations

- urine catecholamines
  - increased catecholamine metabolites (metanephrines) and free catecholamines
  - plasma metanephrines if available (most sensitive)
    - cut-off values will depend on assay used
- CT abdomen
  - if negative, whole body CT and meta-iodo-benzoguanidine (MIBG) scintigraphy, Octreoscan, or MRI

### Treatment

- surgical removal of tumour (curative) with careful pre- and post-operative ICU monitoring
- adequate pre-operative preparation
  - α-blockade for BP control: doxazosin or phenoxybenzamine (these are the most frequently used alpha blockers) (10-21 d pre-operative), IV phentolamine (perioperative, if required)
  - β-blockade for HR control once α blocked for a few days
  - metyrosine (catecholamine synthesis inhibitor) + alpha blocker
  - volume restoration with vigorous salt-loading and fluids
- rescreen urine 1-3 mo post-operatively
- all patients are currently offered genetic testing - probability of germline disease increases with young age, multifocal disease, in the setting of paraganglioma

# Disorders of Multiple Endocrine Glands

## Multiple Endocrine Neoplasia

- neoplastic syndromes involving multiple endocrine glands
- tumours of neuroectodermal origin
- autosomal dominant inheritance with variable penetrance
- genetic screening for RET proto-oncogene on chromosome 10 has long-term benefit in MEN 2
  - early cure and prevention of medullary thyroid cancer

**MEN I – Wermer's Syndrome Affects the 3 Ps**

**P**ituitary
**P**arathyroid
**P**ancreas

**Table 27. MEN Classification**

| Type | Tissues Involved | Clinical Manifestations |
|---|---|---|
| **MEN 1** (chromosome 11) | | |
| **Men 1 (Wermer's Syndrome)**<br><br>**3 Ps (Pituitary, parathyroid and pancreas)** | Pituitary (30-40%)<br>Anterior pituitary adenoma | Headache, visual field defects, often non-secreting but may secrete PRL (most common pituitary functional tumour in MEN 1 leading to galactorrhea, erectile dysfunction, decreased libido, amenorrhea), GH (acromegaly). GH+PRL |
| | Parathyroid (≥95%)<br>Primary hyperparathyroidism from hyperplasia | Nephrolithiasis, bone abnormalities, MSK complaints, symptoms of hypercalcemia |
| | Entero-pancreatic endocrine (30-80%)<br>Pancreatic islet cell tumours<br>Gastrinoma<br>Insulinomas<br>Vasoactive intestinal peptide (VIP)-omas<br>Glucagonoma<br>Carcinoid syndrome | Epigastric pain (peptic ulcers and esophagitis)<br>Hypoglycemia<br>Secretory diarrhea<br><br>Rash (necrolytic migratory erythema), anorexia, anemia, diarrhea, glossitis<br>Flushing, diarrhea, bronchospasm |
| | Adrenal tumours (~40%) | |
| **MEN 2** (chromosome 10) | | |
| 1. Men 2a (Sipple's Syndrome) | Thyroid (>90%)<br>Medullary thyroid cancer (MTC) | Physical signs are variable and often subtle<br><br>Neck mass or thyroid nodule; non-tender, anterior lymph nodes |
| | Adrenal medulla (40-50%)<br>Pheochromocytoma (40-50%) | HTN, palpitations, headache, sweating |
| | Parathyroid (10-20%)<br>1° parathyroid hyperplasia | Symptoms of hypercalcemia |
| | Skin<br>Cutaneous lichen amyloidosis | Scaly skin rash |
| 2. Familial Medullary Thyroid Ca (a variant of 2a) | Thyroid<br>MTC (≥95%) | MTC without other clinical manifestations of MEN 2a or 2b |
| 3. 2b | Thyroid<br>MTC | MTC: most common component, more aggressive and earlier onset than MEN 2a<br>HTN, palpitations, headache, sweating |
| | Adrenal medulla<br>Pheochromocytoma (≥50%) | Chronic constipation; megacolon |
| | Neurons<br>Mucosal neuroma, intestinal ganglioneuromas (100%) | Marfanoid habitus (no aortic abnormalities) |
| | MSK | |

### Investigations

- MEN 1
  - laboratory
    - offer genetic testing to patients with a clinical diagnosis of MEN 1
      - if a mutation is identified, screen family members who are at risk
    - gastrinoma: elevated serum gastrin level (>200 ng/mL) after IV injection of secretin
    - insulinoma: hypoglycemia with insulin and C-peptide levels that are inappropriately high for the level of glucose
    - glucagonoma: elevated glucagon levels
    - pituitary tumours: assess GH, IGF-1, and prolactin levels (for over-production), TSH, free $T_4$, 8 AM cortisol, LH, FSH, bioavailable testosterone or estradiol (for underproduction due to mass effect of tumour)
    - hyperparathyroidism: serum $Ca^{2+}$ and albumin, PTH levels; bone density scan (DEXA)
  - imaging
    - MRI for pituitary tumours, CT or MRI for gastrinoma, CT, MRI, or endoscopic ultrasound for insulinoma

- MEN 2
  - laboratory
    - genetic screening for RET mutations in all index patients
      - if a mutation is identified, screen family members who are at risk
    - calcitonin levels (MTC); urine catecholamines and metanephrines (pheochromocytoma); serum $Ca^{2+}$, and PTH levels (hyperparathyroidism)
    - pentagastrin ± calcium stimulation test if calcitonin level is within reference range
    - FNA for thyroid nodules cytology
  - imaging
    - CT or MRI of adrenal glands to localize pheochromocytoma
    - Metastatic disease generally picked up with cross-sectional imaging

### Treatment

- MEN 1
  - medical
    - proton pump inhibitor (PPI) for acid hypersecretion in gastrinoma
    - cabergoline or other dopamine agonists to suppress prolactin secretion
    - somatostatin analogue for control of symptoms of some of the GI neuroendocrine tumours such as glucagonoma
  - surgery for hyperparathyroidism, insulinoma, glucagonoma, functioning pituitary tumours (except for prolactinomas where dopamine agonists are used, or nonfunctioning pituitary tumours associated with mass effect)
    - trans-sphenoidal approach is generally preferred for pituitary tumours
- MEN 2
  - surgery for MEN 2a associated manifestations may require pre-operative medical therapy
  - prostaglandin inhibitors to alleviate diarrhea associated with thyroid cancer
  - α-blocker for at least 10-21 d for pheochromocytoma pre-operatively
    - hydration, IV bisphosphonates or denosumab for severe hypercalcemia

# Calcium Homeostasis

- normal total serum $Ca^{2+}$: 2.2-2.6 mmol/L
- ionic/free $Ca^{2+}$ levels: 1.15-1.31 mmol/L
- serum $Ca^{2+}$ is 40% protein bound (mostly albumin), 50% ionized, and 10% complexed with $PO_4^{3-}$ and citrate
- regulated mainly by two factors: parathyroid hormone (PTH) and vitamin D, whose actions are on three main organs: GI tract, bone, and kidney



**Primary Hyperparathyroidism**
Increased PTH secretion commonly due to parathyroid adenoma, lithium therapy; less often due to parathyroid carcinoma or parathyroid hyperplasia

**Secondary Hyperparathyroidism**
Partial resistance to PTH action leads to parathyroid gland hyperplasia and increased PTH secretion, often in patients with renal failure and osteomalacia (due to low or low normal serum calcium levels)

**Tertiary Hyperparathyroidism**
Irreversible clonal outgrowth of parathyroid glands, usually in long-standing inadequately treated chronic renal failure on dialysis

**Table 28. Major Regulators in Calcium Homeostasis**

| Major Regulators | Source | Regulation | Net Effect |
|---|---|---|---|
| **PTH** | Parathyroid glands | Stimulated by low serum $Ca^{2+}$ and high serum $PO_4^{3-}$<br>Inhibited by high serum $Ca^{2+}$, high calcitriol, FGF23, and chronic low serum $Mg^{2}$ | ↑ $Ca^{2+}$<br>↑ Cacitriol<br>↓ $PO_4^{3-}$ |
| **Calcitriol ($1,25-(OH)_2D_3$)** | Dietary intake of cholecalciferol (D3) or ergocalciferol (D2)<br>OR<br>Synthesized from cholesterol: UV light on skin makes cholecalciferol (D3). Liver then coverts it to calcidiol ($25-(OH)D_3$) and kidneys convert it to calcitriol | Stimulated by:<br>Low serum $PO_4^{3}$<br>High PTH<br><br>Inhibited by:<br>High serum $PO_4^{3}$<br>Low PTH<br>Calcitriol (negative feedback)<br>FGF23 | ↑ $Ca^{2+}$<br>↑ $PO_4^{3-}$ |
| **Calcitonin** | Thyroid C cells | Stimulated by:<br>Pentagastrin (GI hormone) and high serum $Ca^{2+}$; inhibited by low serum $Ca^{2+}$ | ↓ $Ca^{2+}$ (in pharmacologic doses)<br>↓ $PO_4^{3-}$ |
| **$Mg^{2+}$** | Major intracellular divalent cation | See Nephrology, Serum Magnesium, NP15 | Cofactor for PTH secretion |
| **$PO_4^{3-}$** | Intracellular anion found in all tissues | See Nephrology, Serum Phosphate, NP14 | ↓ $Ca^{2+}$ |

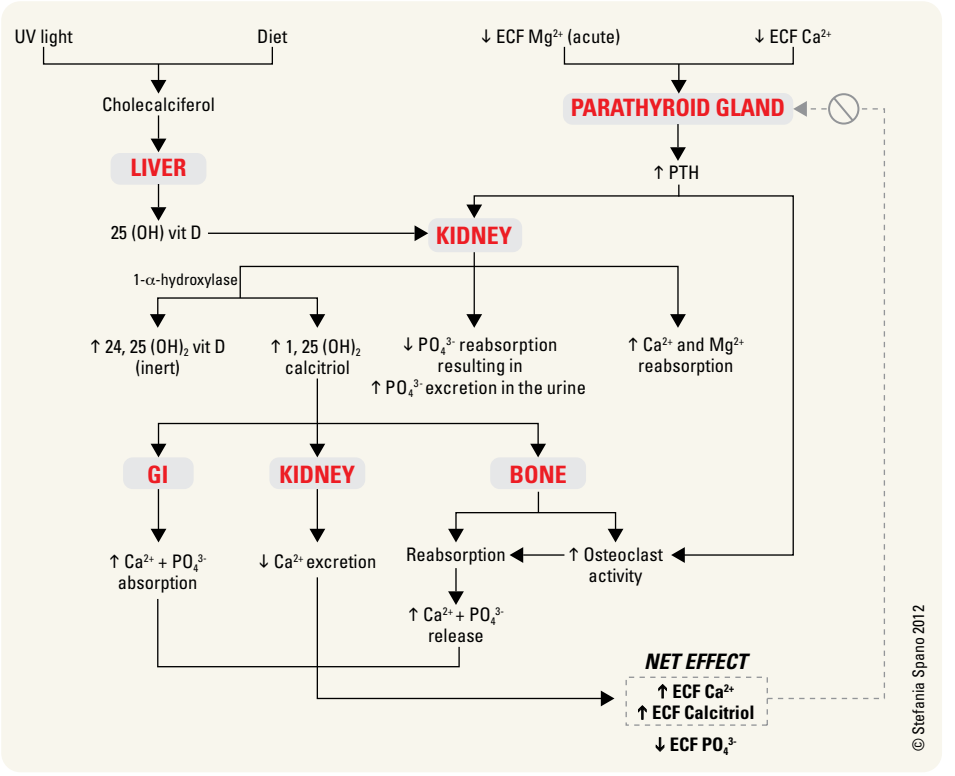



**Figure 16. Parathyroid hormone (PTH) regulation**

**Primary Hyperparathyroidism** is the most common cause of hypercalcemia in healthy outpatients. Most commonly related to a solitary adenoma or less commonly multiple gland hyperplasia. Surgical excision acts as definitive treatment and is recommended for patients who are symptomatic. For mild asymptomatic disease, medical surveillance may be appropriate with annual serum calcium, creatinine, and bone mineral density (BMD)

**For asymptomatic patients, surgery is recommended for those who meet ≥1 of the following criteria:**

- Serum calcium concentration more than 0.25 mmol/L (1.0 mg/dL) above the upper limit of normal
- Creatinine clearance <60 mL/min
- BMD T-score <-2.5 at hip, spine, or distal radius, and/or previous fragility fracture
- Age <50 yr

**Total $Ca^{2+}$ does not reflect ionized $Ca^{2+}$ in the following circumstances:**

- abnormal albumin levels
- critical illness
- chronic hepatic failure/renal failure

In circumstances where the albumin is low, you should perform an ionized calcium assessment.

If ionized calcium is not available, total calcium can be corrected for albumin using this approximation:
Corrected $Ca^{2+}$ (mmol/L) = measured $Ca^{2+}$ + 0.02 (40 – albumin)

- for every decrease in albumin by 10, increase in $Ca^{2+}$ by 0.2

# Hypercalcemia

## Definition

- total corrected serum $Ca^{2+}$ >2.6 mmol/L OR ionized $Ca^{2+}$ >1.35 mmol/L

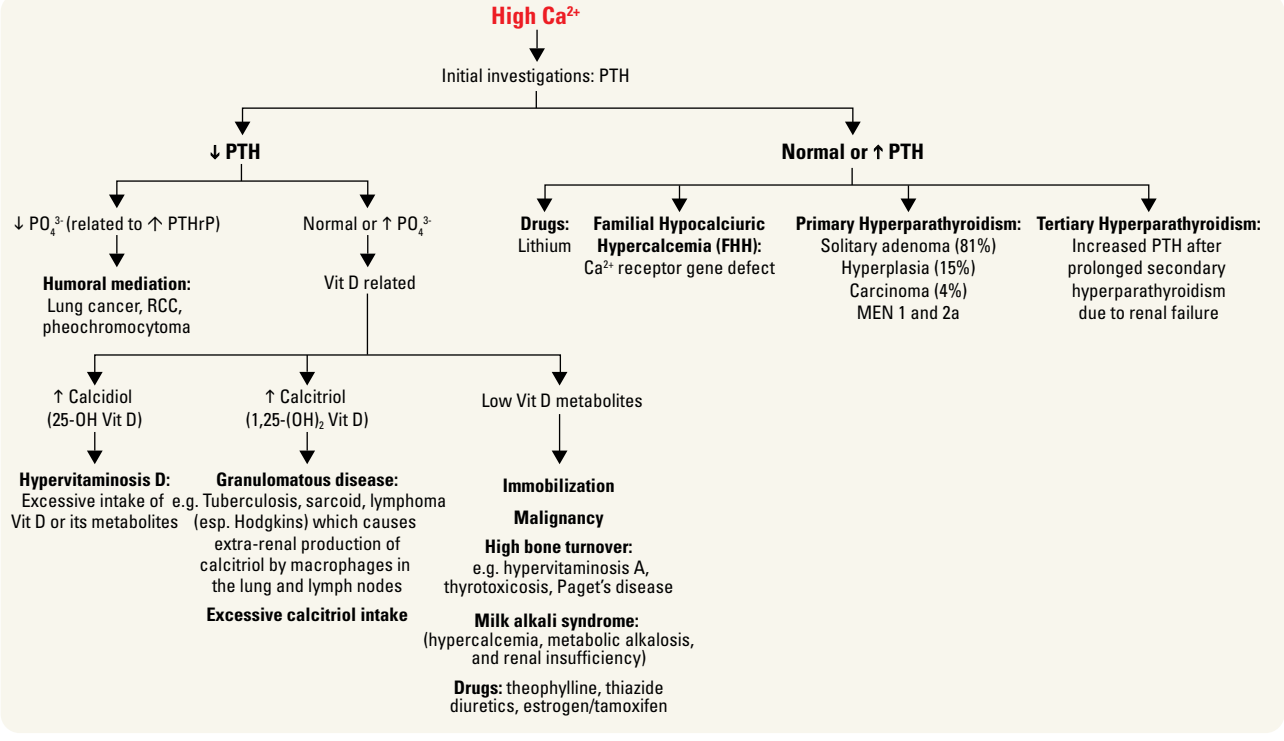



**Figure 17. Differential diagnosis of hypercalcemia**

## Approach to Hypercalcemia

1. Is the patient hypercalcemic?
2. Is the PTH high/normal or low?
3. If PTH is low, is phosphate high/normal or low?
4. If phosphate is high/normal, is the level of vitamin D metabolites high or low?

## Clinical Features

- symptoms depend on the absolute $Ca^{2+}$ value and the rate of its rise (may be asymptomatic)

### Table 29. Symptoms of Hypercalcemia

| Cardiovascular | GI | Renal | Rheumatological | MSK | Psychiatric | Neurologic |
|---|---|---|---|---|---|---|
| HTN<br>Arrhythmia<br>Short QT<br>Deposition of $Ca^{2+}$ on valves, coronary arteries, myocardial fibres | Constipation<br>Anorexia<br>Nausea<br>Vomiting **(groans)**<br>PUD<br>pancreatitis | Polyuria (Nephrogenic DI)<br>Polydipsia<br>**Nephrolithiasis (stones)**<br>Renal failure (irreversible)<br>Dehydration | Gout<br>Pseudogout<br>Chondrocalcinosis | Weakness<br>Bone pain **(bones)** | >3 mmol/L (12 mg/dL)<br>Increased alertness<br>Anxiety<br>Depression<br>Cognitive dysfunction<br>Organic brain syndromes<br>>4 mmol/L (16 mg/dL)<br>**Psychosis (moans)** | Hypotonia<br>Hyporeflexia<br>Myopathy<br>Paresis |

** **Hypercalcemic crisis (usually >4 mmol/L or 16 mg/dL):** primary symptoms include oliguria/anuria and mental status changes including somnolence and eventually coma → this is a medical emergency and should be treated immediately!

## Treatment

- treatment depends on the $Ca^{2+}$ level and the symptoms
- treat the underlying cause of the hypercalcemia
- treat acute, symptomatic hypercalcemia aggressively
- mild asymptomatic hypercalcemia: monitor, avoid: thiazide, volume depletion, high $Ca^{2+}$ diet, lithium, bed rest

### Table 30. Treatment of Acute Hypercalcemia/Hypercalcemic Crisis

| | |
|---|---|
| **Increase Urinary $Ca^{2+}$ Excretion** | FLUID, FLUID, FLUID!<br>Isotonic saline (4-5 L) over 24 h ± loop diuretic (e.g. furosemide) but only if hypervolemic (urine output >200mL/h)<br>Calcitonin:<br>4 IU/kg IM/SC q12h<br>8 IU/kg IM/SC q6h<br>Only works for 48 h, can develop tachyphylaxis<br>Rapid onset within 4-6 h<br>Before prescribing Calcitonin, remember to ask about fish allergies |
| **Diminish Bone Resorption** | Bisphosphonates (treatment of choice)<br>Inhibits osteoclastic bone resorption, preventing calcium release from bone<br>Effects on calcium levels are typically seen at 24-48 h after administration<br>Calcitonin often given in conjunction with bisphosphonate, given rapid onset of effect<br>Indicated in malignancy-related hypercalcemia (IV pamidronate or zoledronic acid used) |
| **Decrease GI $Ca^{2+}$ Absorption** | Corticosteroids can be used in hypercalcemia mediated by 1,25 Vitamin D. Corticosteroids are potent inhibitors of 1a-hydroxylase and therefore, decrease calcitriol production by activated mononuclear cells (e.g. in lymphoma, granuloma)<br>Effects will be seen in 2-5 d |
| **Dialysis** | Treatment of last resort<br>Indication: severe malignancy-associated hypercalcemia and renal insufficiency or heart failure |

# Hypocalcemia

## Definition

- total corrected serum $Ca^{2+}$ <2.2 mmol/L

### Table 31. Clinical Features of Hypocalcemia

| Acute Hypocalcemia | Chronic Hypocalcemia |
|---|---|
| Paresthesia<br>Laryngospasm (with stridor)<br>Hyperreflexia<br>Tetany<br>Chvostek's sign (tap CN VII)<br>Trousseau's sign (carpal spasm)<br>ECG changes<br>Delirium<br>Psychiatric Sx: emotional instability, anxiety, and depression<br><br>Note: Tetany is a hallmark of hypocalcemia – can be mild or severe<br><br>Mild: perioral numbness, paresthesia of hands and feet, muscle spasm<br>Severe: carpopaedal spasm, laryngospasm, focal/generalized seizures | CNS: lethargy, seizures, psychosis, basal ganglia calcification, Parkinson's, dystonia, hemiballismus, papilledema, pseudotumour cerebri<br>CVS: prolonged QT interval → Torsades de pointes (ventricular tachycardia)<br>GI: steatorrhea<br>ENDO: impaired insulin release<br>SKIN: dry, scaling, alopecia, brittle and transversely fissured nails, candidiasis, abnormal dentition<br>OCULAR: cataracts<br>MSK: generalized muscle weakness and wasting |



The symptoms and signs of hypercalcemia include:
**"Bones, stones, groans, and psychiatric overtones"**



The most common cause of **hypercalcemia in hospital** is **malignancy-associated hypercalcemia**
- Usually occurs in the later stages of disease
- Most commonly seen in lung, renal, breast, ovarian, and squamous tumours, as well as lymphoma and multiple myeloma

Mechanisms:
- Secretion of parathyroid hormone-related protein (PTHrP) which mimics PTH action by preventing renal calcium excretion and activating osteoclast-induced bone resorption
- Cytokines in multiple myeloma
- Calcitriol production by lymphoma
- Osteolytic bone metastases direct effect
- Excess PTH in parathyroid cancer



Before prescribing Calcitonin, remember to ask about fish allergies



**Differential Diagnosis of Hypercalcemia**
- Primary hyperparathyroidism
- Malignancy: hematologic, humoral, skeletal metastases (>90% from 1 or 2)
- Renal disease: tertiary hyperparathyroidism
- Drugs: calcium carbonate, milk alkali syndrome, thiazide, lithium, theophylline, vitamin A/D intoxication
- Familial hypocalciuric hypercalcemia
- Granulomatous disease: sarcoidosis, tuberculosis, Hodgkin's lymphoma
- Thyroid disease: thyrotoxicosis
- Adrenal disease: adrenal insufficiency, pheochromocytoma
- Immobilization



**Signs and Symptoms of Acute Hypocalcemia**
- **Paresthesias**: perioral, hands, and feet
- **Chvostek's sign**: percussion of the facial nerve just anterior to the external auditory meatus elicits ipsilateral spasm of the orbicularis oculi or orbicularis oris muscles
- **Trousseau's sign**: inflation of a blood pressure cuff above systolic pressure for 3 min elicits carpal spasm and paresthesia



Hypomagnesmia can impair PTH secretion and action



**Watch Out for:**
- Volume depletion via diuresis
- Arrhythmias

## Approach to Hypocalcemia

1. Is the patient hypocalcemic?
2. Is the PTH high or low?
3. If PTH is high, is phosphate low or normal?
4. Is the $Mg^{2+}$ level low?

## Approach to Treatment

- correct underlying disorder
- treat concurrent hypomagnesemia
- mild and symptomatic (ionized $Ca^{2+}$ >0.8 mmol/L)
  - calcium supplementation - 1500-2000 mg of elemental calcium/d
  - calcitriol 0.25 µg/d (especially in renal failure or hypoparathyroidism)
- note: this dose is typically higher in hypoparathyroidism
- acute or symptomatic hypocalcemia (ionized $Ca^{2+}$ <0.7 mmol/L)
  - immediate treatment required
  - IV calcium gluconate 1-2 g over 10-20 min followed by slow infusion
  - if underlying cause is hypoparathyroidism, the goal is to raise $Ca^{2+}$ to low normal range (2.0-2.1 mmol/L) to prevent symptoms but allow maximum stimulation of PTH secretion
- if PTH recovery not expected, requires long-term therapy with calcitriol and calcium
- start oral calcium and calcitriol concurrently with IV calcium infusion
- do not correct hypocalcemia if asymptomatic and suspected to be transient

**Acute Management of Hypercalcemia/ Hypercalcemic Crisis**

- Volume expansion (e.g. NS IV 300-500 cc/h): initial therapy
- Calcitonin: transient, partial response
- Bisphosphonate: treatment of choice, adjust dose if CrCl <30 ml/min
- Corticosteroid: most useful in vitamin D toxicity, granulomatous disease, some malignancies
- Saline diuresis + loop diuretic (for volume overload): temporary measure

**Differential Diagnosis of Tetany**

- Hypocalcemia
- Metabolic alkalosis (with hyperventilation)
- Hypokalemia
- Hypomagnesemia

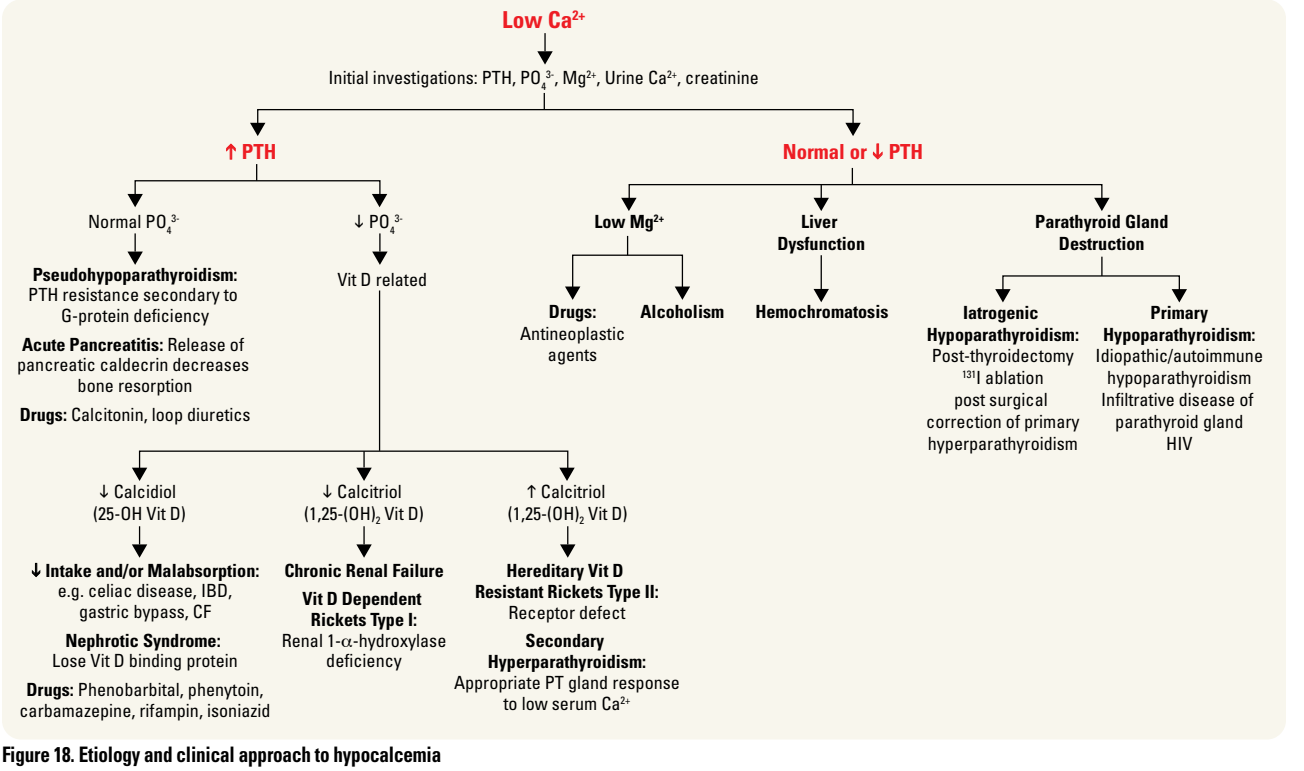



**Figure 18. Etiology and clinical approach to hypocalcemia**

Transient hypoparathyroidism (resulting in hypocalcemia) common after subtotal thyroidectomy (permanent in <3% of surgeries)

**Online Clinical Tools**
**CAROC**
www.osteoporosis.ca/multimedia/pdf/CAROC.pdf
**FRAX**
www.shef.ac.uk/FRAX/tool.aspx

# Metabolic Bone Disease

- see 2010 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis for details

## Osteoporosis

### Definition

- a condition characterized by decreased bone mass and microarchitectural deterioration with a consequent increase in bone fragility and susceptibility to fracture
- BMD is measured at hip and lumbar spine, BMD T-score ≤-2.5 is indicative of osteoporosis
- osteopenia (low bone mass): BMD with T-score between –1.0 and –2.5

### ETIOLOGY AND PATHOPHYSIOLOGY

### Secondary Osteoporosis

- gastrointestinal diseases
  - gastrectomy
  - malabsorption (e.g. celiac disease)
  - chronic liver disease
- bone marrow disorders
  - multiple myeloma
  - lymphoma
  - leukemia
- endocrinopathies
  - Cushing's syndrome
  - hyperparathyroidism
  - hyperthyroidism
  - premature menopause
  - DM
  - hypogonadism
- malignancy
  - secondary to chemotherapy
  - myeloma
- drugs
  - corticosteroid therapy
  - phenytoin
  - chronic heparin therapy
  - androgen deprivation therapy
  - aromatase inhibitors
  - rheumatologic disorders
    - rheumatoid arthritis
    - SLE
    - ankylosing spondylitis
  - renal disease
  - poor nutrition
  - immobilization
- COPD (due to disease, tobacco, and glucocorticoid use)

### Clinical Features

- commonly asymptomatic
- height loss due to collapsed vertebrae
- fractures: most commonly in hip, vertebrae, humerus, and wrist
  - fragility fractures: fracture with fall from standing height or less
  - Dowager's hump: collapse fracture of vertebral bodies in mid-dorsal region
  - x-ray: vertebral compression fractures (described as wedge fractures, require a minimum of 20% height loss), "codfishing" sign (weakening of subchondral plates and expansion of intervertebral discs)
- pain, especially backache, associated with fractures

### Approach to Osteoporosis

1. assess risk factors for osteoporosis on history and physical
2. decide if patient requires BMD testing with dual-energy x-ray absorptiometry (DEXA): men and women ≥65 yr (or younger if presence of risk factors, see Table 33, E44)
3. initial investigations
   - all patients with osteoporosis: calcium corrected for albumin, CBC, creatinine, ALP, TSH
   - also consider serum and urine protein electrophoresis if vertebral fractures, celiac workup, and 24 h urinary $Ca^{2+}$ excretion to rule out additional secondary causes
   - 25-OH-Vitamin D level should only be measured after 3-4 mo of adequate supplementation and should not be repeated if an optimal level ≥75 nmol/L is achieved
   - lateral thoracic and lumbar x-ray if clinical evidence of vertebral fracture (or in individuals at moderate risk of fracture to help decide if they require medical therapy)
4. assess 10-yr fracture risk by combining BMD result and risk factors
   1) WHO Fracture Risk Assessment Tool (FRAX)
   2) Canadian Association of Radiologists and Osteoporosis Canada Risk Assessment Tool (CAROC)
      - approach to management guided by 10-yr risk stratification into low, medium, high risk
5. for all patients being assessed for osteoporosis, encourage appropriate lifestyle changes (see Table 34, E44)



**Corticosteroid Therapy is a Common Cause of Secondary Osteoporosis**
Individuals receiving ≥7.5 mg of prednisone daily for over 3 mo should be assessed for bone-sparing therapy
Mechanism: increased resorption + decreased formation + increased urinary calcium loss + decreased intestinal calcium absorption + decreased sex steroid production



**Calcium Plus Vitamin D Supplementation and Risk of Fractures. Osteoporosis**
Int 2015;27:367-376
**Purpose**: To review trials of Vitamin D and Calcium therapy for reducing fracture risk in osteoporosis.
**Study**: Systematic review searching 2011-2015, inclusive, identified 8 RCTs totalling 30,970 participants. RCTs reviewed included healthy adults and ambulatory older adults with medical conditions (excluding cancer). Vitamin D and Calcium combination therapy was compared to placebo.
**Results**: Analysis of RCT data revealed that calcium plus vitamin D supplementation produced a statistically significant reduction in risk of total fractures (0.85; CI:0.73-0.98) and in hip fractures (0.70; CI:0.56-0.87). Subgroup analysis was significant for community dwelling or institutionalized patients.
**Conclusions**: Systematic analysis suggests that Vitamin D and calcium therapy significantly decreases fracture risk. This study did not specifically look at individuals with osteoporosis. However, it still supports that Vitamin D and calcium should continue to be used as preventative treatment for individuals at increased risk of fractures.



**Clinical Signs of Fractures or Osteoporosis**
- Height loss >3 cm (Sn 92%)
- Weight <51 kg
- Kyphosis (Sp 92%)
- Tooth count <20 (Sp 92%)
- Grip strength
- Armspan-height difference >5 cm (Sp 76%)
- Wall-occiput distance >0 cm (Sp 87%)
- Rib-pelvis distance ≤2 finger breadth (Sn 88%)

### Table 32. Indications for BMD Testing

| Older Adults (age ≥50 yr) | Younger Adults (age <50 yr) |
|---|---|
| All women and men age ≥65 yr<br>Menopausal women, and men aged 50-64 yr with clinical risk factors for fracture:<br>Fragility fracture after age 40<br>Prolonged glucocorticoid use<br>Other high-risk medication use (aromatase inhibitors, androgen deprivation therapy)<br>Parental hip fracture<br>Vertebral fracture or osteopenia identified on x-ray<br>Current smoking<br>High alcohol intake<br>Low body weight (<60 kg) or major weight loss (>10% of weight at age 25 yr)<br>Rheumatoid arthritis<br>Other disorders strongly associated with osteoporosis: primary hyperparathyroidism, T1DM, osteogenesis imperfecta, uncontrolled hyperthyroidism, hypogonadism or premature menopause (<45 yr), Cushing's disease, chronic malnutrition or malabsorption, chronic liver disease, COPD, and chronic inflammatory conditions (e.g. inflammatory bowel disease) | Fragility fracture<br>Prolonged use of glucocorticoids<br>Use of other high-risk medications (aromatase inhibitors, androgen deprivation therapy, anticonvulsants)<br>Hypogonadism or premature menopause<br>Malabsorption syndrome<br>Primary hyperparathyroidism<br>Other disorders strongly associated with rapid bone loss and/or fracture |

### Table 33. Osteoporosis Risk Stratification

| | |
|---|---|
| **Low Risk** | |
| 10 yr fracture risk <10% | Unlikely to benefit from pharmacotherapy; encourage lifestyle changes<br>Reassess risk in 5 yr |
| **Medium Risk** | |
| 10 yr fracture risk 10-20% | Discuss patient preference for management and consider additional risk factors<br>Factors that warrant consideration for pharmacological therapy:<br>Additional vertebral fracture(s) identified on vertebral fracture assessment (VFA) or lateral spine x-ray<br>Previous wrist fracture in individuals ≥65 or with T-score ≤–2.5<br>Lumbar spine T-score much lower than femoral neck T-score<br>Rapid bone loss<br>Men receiving androgen-deprivation therapy for prostate cancer<br>Women receiving aromatase-inhibitor therapy for breast cancer<br>Long-term or repeated systemic glucocorticoid use (oral or parenteral) that does not meet the conventional criteria for recent prolonged systemic glucocorticoid use<br>Recurrent falls (defined as falling 2 or more times in the past 12 mo)<br>Other disorders strongly associated with osteoporosis<br><br>Repeat BMD and reassess risk every 1-3 yr initially |
| **High Risk** | |
| 10 yr fracture risk >20%; OR<br>Prior fragility fracture of hip or spine; OR<br>More than one fragility fracture | Start pharmacotherapy |

**Aledronate (10 mg/d)**

| | |
|---|---|
| 1° Prevention – Vertebral (Gold) | 45% RRR, 2% ARR |
| 1° Prevention – Hip | Not significant |
| 1° Prevention – Wrist | Not significant |
| 2° Prevention – Vertebral (Gold) | 45% RRR, 6% ARR |
| 2° Prevention – Hip (Gold) | 53% RRR, 1% ARR |
| 2° Prevention – Wrist (Gold) | 50% RRR, 2% ARR |

**Etidronate (400 mg/d)**

| | |
|---|---|
| 1° Prevention – Vertebral | Not significant |
| 1° Prevention – Hip | Not significant |
| 1° Prevention – Wrist | Not significant |
| 2° Prevention – Vertebral (Silver) | 47% RRR, 5% ARR |
| 2° Prevention – Hip | No benefit |
| 2° Prevention – Wrist | No benefit |

**Risedronate (5 mg/d)**

| | |
|---|---|
| 1° Prevention – Vertebral | Not significant |
| 1° Prevention – Hip | Not significant |
| 1° Prevention – Wrist | Not significant |
| 2° Prevention – Vertebral (Gold) | 39% RRR, 5% ARR |
| 2° Prevention – Hip (Silver) | 26% RRR, 1% ARR |
| 2° Prevention – Wrist | Not significant |

## Treatment of Osteoporosis

### Table 34. Treatment of Osteoporosis in Women and Men

| | |
|---|---|
| **Treatment for Both Men and Women** | |
| **Lifestyle** | Diet: Elemental calcium 1000-1200 mg/d; Vit D 1000 IU/d<br>Exercise: 3x30 min weight-bearing exercises, balance exercise, and aerobic exercise/wk<br>Cessation of smoking, reduce caffeine intake<br>Stop/avoid osteoporosis-inducing medications |
| **Drug Therapy** | |
| **Bisphosphonate**: inhibitors of osteoclast binding | 1st line in prevention of hip, nonvertebral, and vertebral # (Grade A): alendronate (PO), risedronate (PO), zoledronic acid (IV) |
| **RANKL Inhibitors** | Denosumab: 1st line in prevention of hip, nonvertebral, vertebral # (Grade A)<br>*Denosumab should not be abruptly stopped/administration delayed. Increased risk of vertebral fractures due to increased bone turnover on discontinuation |
| **Parathyroid Hormone (teriparatide)** | 18-24 mo duration, followed by long-term anti-resorptive therapy with bisphosphonate or RANKL inhibitor, followed by long-term anti-resorptive therapy with bisphosphonate or RANKL inhibitor |
| **Treatment Specific to Post-Menopausal Women** | |
| **SERM (selective estrogen-receptor modulator):** agonistic effect on bone but antagonistic effect on uterus and breast | Raloxifene: 1st line in prevention of vertebral # (Grade A)<br>+ve: prevents osteoporotic # (Grade A to B evidence), improves lipid profile, decreased breast cancer risk<br>-ve: increased risk of DVT/PE, stroke mortality, hot flashes, leg cramps |
| HRT: combined estrogen + progesterone (see Gynecology, GY34) | 1st line in prevention of hip, nonvertebral, and vertebral # (Grade A)<br>For most women, risks > benefits<br>Combined estrogen/progestin prevents hip, vertebral, total #<br>Increased risks of breast cancer, cardiovascular events, and DVT/PE |

**Factors Necessary for Mineralization**

- Quantitatively and qualitatively normal osteoid formation
- Normal concentration of calcium and phosphate in ECF
- Adequate bioactivity of ALP
- Normal pH at site of calcification
- Absence of inhibitors of calcification

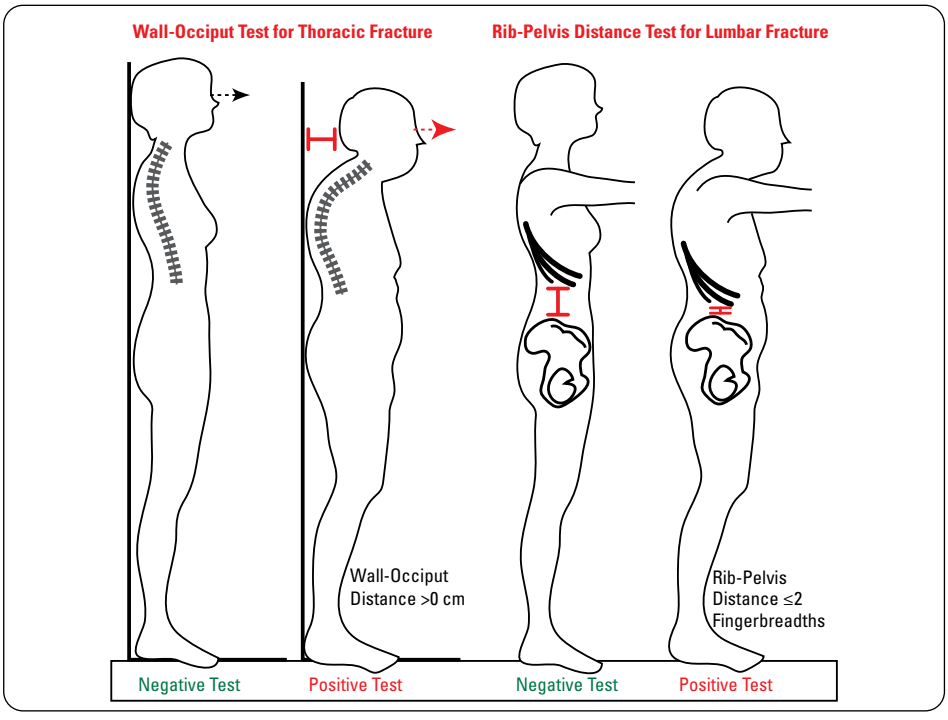



**Figure 19. Physical examination test**

# Osteomalacia and Rickets

- osteopenia with disordered calcification leading to a higher proportion of osteoid (unmineralized) tissue prior to epiphyseal closure: rickets (in childhood), osteomalacia (in adulthood)

## Etiology and Pathophysiology

### Vitamin D Deficiency

- deficient uptake or absorption
  - nutritional deficiency
  - malabsorption: post-gastrectomy, small bowel disease (e.g. Celiac sprue), pancreatic insufficiency
- defective 25-hydroxylation
  - liver disease
  - anticonvulsant therapy (phenytoin, carbamazepine, phenobarbital)
- loss of vitamin D binding protein
  - nephrotic syndrome
- defective 1-α-25 hydroxylation
  - hypoparathyroidism
- renal failure
- pathophysiology: leads to secondary hyperparathyroidism and hypophosphatemia

### Mineralization Defect

- abnormal matrix
  - osteogenesis imperfecta
- enzyme deficiency
  - hypophosphatasia (inadequate ALP bioactivity)
- presence of calcification inhibitors
  - aluminum, high dose fluoride, anticonvulsants

**Table 35. Clinical Features of Rickets and Osteomalacia**

| Rickets | Osteomalacia |
|---|---|
| Skeletal pain and deformities, bow legged | Not as dramatic |
| Fracture susceptibility | Diffuse skeletal pain |
| Weakness and hypotonia | Bone tenderness |
| Disturbed growth | Fractures |
| Ricketic rosary (prominent costochondral junctions) | Gait disturbances (waddling) |
| Harrison's groove (indentation of lower ribs) | Proximal muscle weakness |
| Hypocalcemia | Hypotonia |

### Investigations

**Table 36. Laboratory Findings in Osteomalacia and Rickets**

| Disorder | Serum Phosphate | Serum Calcium | Serum ALP | Other Features |
|---|---|---|---|---|
| **Vitamin D deficiency** | Decreased | Decreased to normal | Increased | Decreased calcitriol |
| **Hypophosphatemia** | Decreased | Normal | Decreased to normal | |
| **Proximal RTA** | Decreased | Normal | Normal | Associated with hyperchloremic metabolic acidosis |
| **Conditions associated with abnormal matrix formation** | Normal | Normal | Normal | |

- radiologic findings
  - pseudofractures, fissures, narrow radiolucent lines – thought to be healed stress fractures or the result of erosion by arterial pulsation
  - loss of distinctness of vertebral body trabeculae; concavity of the vertebral bodies
  - changes due to secondary hyperparathyroidism: subperiosteal resorption of the phalanges, bone cysts, resorption of the distal ends of long bones
  - others: bowing of tibia, coxa profundus hip deformity
- bone biopsy: usually not necessary but considered the gold standard for diagnosis

### Treatment
- definitive treatment depends on the underlying cause
- vitamin D supplementation
- $PO_4^{3-}$ supplements if low serum $PO_4^{3-}$, $Ca^{2+}$ supplements for isolated calcium deficiency
- bicarbonate if chronic metabolic acidosis

**KDIGO 2017 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease**
Kidney Inter Suppl 2017;7(1):1-60

**Recommendations for Metabolic Bone Disease in CKD**

**Screening**
- In CKD patients with evidence of CKD-MBD and/or risk factors for osteoporosis, perform BMD testing to assess fracture risk if results will impact treatment decisions
- In patients with CKD-BMD, it is reasonable to perform a bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions

**Management**
- Treatment of CKD-MBD should be based on serial assessments of $PO_4^{3-}$, $Ca^{2+}$ and PTH levels, considered together
- Suggest lowering elevated $PO_4^{3-}$ levels towards the normal range
- Avoid hyperglycemia in adult patients and maintain serum $Ca^{+}$ in age-appropriate normal range in children

## Renal Osteodystrophy

- changes to mineral metabolism and bone structure secondary to chronic kidney disease
- represents a mixture of four types of bone disease:
  - osteomalacia: low bone turnover combined with increased unmineralized bone (osteoid)
  - adynamic bone disease: low bone turnover due to excessive suppression of parathyroid gland
  - osteitis fibrosa cystica: increased bone turnover due to secondary hyperparathyroidism
  - mixed uremic osteodystrophy: both high and low bone turnover, characterized by marrow fibrosis and increased osteoids
- metastatic calcification secondary to hyperphosphatemia may occur

### Pathophysiology
- metabolic bone disease secondary to chronic renal failure
- combination of hyperphosphatemia (inhibits 1,25(OH)2-Vit D synthesis) and loss of renal mass (reduced 1-α-hydroxylase)

### Clinical Features
- soft tissue calcifications, necrotic skin lesions if vessels involved
- osteodystrophy, generalized bone pain and fractures
- pruritus
- neuromuscular irritability and tetany may occur (with low serum calcium)
- radiologic features of osteitis fibrosa cystica, osteomalacia, osteosclerosis, osteoporosis

### Investigations
- serum $Ca^{2+}$ corrected for albumin, $PO_4^{3-}$, PTH, ALP, ± imaging (x-ray, BMD), ± bone biopsy

### Treatment
- prevention
- maintenance of normal serum $Ca^{2+}$ and $PO_4^{3-}$ by restricting $PO_4^{3-}$ intake to 1 g OD
- $Ca^{2+}$ supplements; $PO_4^{3-}$ binding agents (calcium carbonate, aluminum hydroxide)
- vitamin D with close monitoring to avoid hypercalcemia and metastatic calcification

## Paget's Disease of Bone

### Definition
- a metabolic disease characterized by excessive bone destruction and repair

### Epidemiology
- 3% of the population, 10% of population >80 yr old
- consider Paget's disease of bone in older adults with ↑ ALP but normal GGT

### Etiology and Pathophysiology
- postulated to be related to a slowly progressing viral infection of osteoclasts, possibly paramyxovirus
- strong familial incidence
- initiated by increased osteoclastic activity leading to increased bone resorption; osteoblastic activity increases in response to produce new bone that is structurally abnormal and fragile

### Differential Diagnosis
- osteogenic sarcoma
- multiple myeloma
- fibrous dysplasia
- osteitis fibrosa cystica
- metastases

### Clinical Features
- usually asymptomatic (routine x-ray finding or elevated serum ALP)
- 3 characteristic findings: osteolytic lesions, cortical thickening, pseudofractures (small fissures which develop in the convex surface of long bone)
- most commonly affects: skull, thoracolumbar spine, pelvis, and long bones of lower extremities
- severe bone pain (e.g. pelvis, femur, tibia)
- skeletal deformities: bowed tibias, kyphosis, frequent fractures
- increased risk of osteosarcoma and giant cell tumours

### Investigations
- laboratory
  - high serum ALP, normal or high $Ca^{2+}$, normal $PO_4^{3-}$
  - elevated c-telopeptide (CTX) (bone resorption marker, breakdown product of collagen in the blood)
- imaging
  - confirmation on x-ray required for diagnosis
    - denser bone with cortical thickening
    - characteristic findings: osteolytic lesions, cortical thickening & pseudofractures
    - Paget disease-related signs include: Tam o'Shanter sign (appearance of advanced Paget disease of the skull – overall enlargement of cranium, skull falling over the facial bones), blade of grass sign (lucent leading edge in a long bone seen in lytic phase of Paget's), osteoporosis circumscripta (radiolucent regions of the skull), jigsaw pattern bone or mosaic pattern bone (thickened, disorganized trabeculae lead to areas of sclerosis), picture frame vertebra (cortex of vertebral body is thickened), cotton wool appearance of bone (results from thickened, disorganized trabeculae that lead to areas of sclerosis), banana fracture (horizontal pathological fracture seen in bones deformed by Paget's), looser zones (wide, transverse lucencies traversing through a bone), ivory vertebra sign (diffuse and homogenous increase in opacity of a vertebral body)
    - Burned-out Paget's disease: when the disease has been there for a long time
  - bone scan to evaluate the extent of disease and identify asymptomatic sites

### Complications
- local
  - fractures; osteoarthritis
  - cranial nerve compression and palsies (e.g. deafness), spinal cord compression
  - osteosarcoma/sarcomatous change in 1-3%
    - indicated by marked bone pain, new lytic lesions and suddenly increased ALP
- systemic
  - hypercalcemia and nephrolithiasis
  - high output CHF due to increased vascularity

### Treatment
- goals: decrease pain, decrease rate of remodelling
- weight-bearing exercise
- adequate calcium and vitamin D intake to prevent development of secondary hyperparathyroidism
- treat medically if symptomatic or asymptomatic with ALP >3x normal or planned surgery
  - bisphosphonates, e.g. zoledronic acid 5 mg IV per yr (preferred) OR alendronate 40 mg PO OD x 6 mo OR risedronate 30 mg PO OD x 3 mo
  - calcitonin 50-100 U/d SC if unable to tolerate bisphosphonate
- surgery for fractures, deformity, degenerative changes

# Male Reproductive Endocrinology

## Androgen Regulation

- testosterone (from Leydig cells) primarily involved in negative feedback on LH and GnRH, whereas inhibin (from Sertoli cells) suppresses FSH secretion

## Tests of Testicular Function

- testicular size (lower limit = 4 cm x 2.5 cm in adult). Can use orchidometer to measure testicular volume (12-25 ml = adult size)
- LH, FSH, total, bioavailable, and/or free testosterone
- semen analysis
  - semen volume, sperm concentration, morphology, and motility are the most commonly used parameters
- testicular biopsy
  - indicated with normal FSH and azoospermia/oligospermia

## Hypogonadism and Infertility

- see Urology, U36
- deficiency in gametogenesis or testosterone production

### Etiology

- causes include primary (testicular failure), secondary (hypothalamic-pituitary failure), and idiopathic

### Diagnosis of Testosterone Deficiency Syndrome (i.e. adult onset primary hypogonadism)

- requires clinical manifestations of testosterone deficiency (see sidebar) AND documented testosterone levels below the laboratory reference range (confirmed on x2 separate analyses, test needs to be done at 8-9 AM when testosterone is usually at its peak)
- rule out secondary causes

**Table 37. Classification and Features of Hypogonadism**

| | Hypergonadotropic Hypogonadism (Primary Hypogonadism) | Hypogonadotropic Hypogonadism (Secondary Hypogonadism) |
|---|---|---|
| **Definition** | Primary testicular failure<br>↑ LH and FSH<br>↓ testosterone and sperm count | Hypothalamic-pituitary axis failure<br>↓ LH + FSH (LH sometimes inappropriately normal)<br>↓ testosterone and sperm count |
| **Etiology** | Congenital<br>Chromosomal defects (Klinefelter's, Noonan)<br>Cryptorchidism<br>Disorders of sexual development (DSD)<br>Bilateral anorchia (vanishing testicle syndrome)<br>Myotonic dystrophy<br>Mutation of FSH or LH receptor gene<br>Disorders of androgen synthesis<br>Germ cell defects<br>Sertoli cell only syndrome<br>Leydig cell aplasia/failure<br>Infection/Inflammation<br>Orchitis – tuberculosis, lymphoma, mumps, leprosy<br>Genital tract infection<br>Physical factors<br>Trauma, heat, irradiation, testicular torsion, varicocele<br>Drugs<br>Marijuana, alcohol, chemotherapy, ketoconazole, glucocorticoid, spironolactone | Congenital<br>Kallman's syndrome<br>Prader-Willi syndrome<br>Abnormal subunit of LH or FSH<br>Infection<br>Tuberculosis, meningitis<br>Endocrine<br>Adrenal androgen excess<br>Cushing's syndrome<br>Hypo or hyperthyroidism<br>Hypothalamic-pituitary disease (tumour, hyperprolactinemia, hypopituitarism)<br>Drugs<br>Alcohol, marijuana, spironolactone, ketoconazole, GnRH agonists, androgen/estrogen/progestin use, chronic narcotic use<br>Chronic illness<br>Cirrhosis, chronic renal failure, AIDS<br>Sarcoidosis, Langerhan's cell histiocytosis, hemochromatosis<br>Critical illness<br>Surgery, MI, head trauma<br>Obesity<br>Idiopathic |
| **Diagnosis** | **Testicular size and consistency (soft/firm)**<br>Sperm count<br>LH, FSH, total, and/or bioavailable testosterone<br>hCG stimulation (mainly used in pediatrics)<br>Karyotype | **Testicular size and consistency (soft/firm)**<br>Sperm count<br>LH, FSH, total, and/or bioavailable testosterone<br>Prolactin levels (and pituitary panel - T4/8AM cortisol)<br>Fe, Transferrin<br>MRI of hypothalamic-pituitary region |

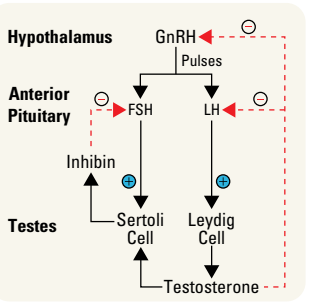



**Figure 20. Hypothalamo-pituitary-gonadal axis**

**Two Distinct Features of Primary Hypogonadism**

- The decrease in sperm count is affected to a greater extent than the decrease in serum testosterone level
- Likely to be associated with gynecomastia

**Two Features of Secondary Hypogonadism**

- Associated with an equivalent decrease in sperm count and serum testosterone
- Less likely to be associated with gynecomastia

### Treatment
- goal: testosterone replacement (improve libido, muscle mass, strength, body hair growth, bone mass)
  - IM injection, transdermal testosterone patch/gel, oral
  - side effects: acne, fluid retention, erythrocytosis, sleep apnea, benign prostatic hypertrophy, uncertain effects on cardiac events/mortality in older men
  - contraindicated in men with prostate or breast cancer, a palpable prostate nodule, PSA>4 ng/mL, elevated hematocrit, untreated severe OSA, severe LUTS, uncontrolled CHF, MI or stroke in last 6 mo, or thrombophilia
  - not suggested in men >65, in men with T2DM with low testosterone concentrations, or in men planning fertility in the near term
  - testosterone therapy only to treat symptoms of hypogonadism, often results in decreased spermatogenesis by further suppression of hypothalamic-pituitary-gonad axis
- goal: fertility
  - treat underlying cause
  - GnRH agonist if hypothalamic dysfunction with intact pituitary, administered SC in pulsatile fashion using an external pump
  - hCG ± recombinant follicular stimulating hormone (rFSH) in cases of either hypothalamic or pituitary lesions
  - dopamine agonist (e.g. bromocriptine, cabergoline) if prolactinoma
  - testicular sperm extraction (TESE) or microscopic sperm extraction (MICROTESE) – only if testicular tissues are not functioning

### Other Causes of Male Infertility
- hereditary disorders: Kartagener syndrome (primary ciliary dyskinesia), cystic fibrosis (absence of the vas deferens)
- anatomy: hypospadias, retrograde ejaculation
- obstruction: vasal occlusion, vasal aplasia, vasectomy, seminal vesicle disease
- sexual dysfunction: erectile dysfunction, premature ejaculation, infrequent coitus
- surgery: TURP, radical prostatectomy, orchiectomy

## DEFECTS IN ANDROGEN ACTION

### Etiology
- complete androgen insensitivity (CAIS)
- partial androgen insensitivity (PAIS)
- 5-α-reductase deficiency
- mixed gonadal dysgenesis
- defects in testosterone synthesis
- infertile male syndrome
- undervirilized fertile male syndrome

### Clinical Features
- depends on age of onset

**Table 38. Effects of Testosterone Deficiency**

| | |
|---|---|
| **First Trimester *in utero*** | Incomplete virilization of external genitalia (ambiguous genitalia)<br>Incomplete development of Wolffian ducts to form male internal genitalia (male pseudohermaphrodism) |
| **Third Trimester *in utero*** | Micropenis<br>Cryptorchidism (failure of normal testicular descent) |
| **Prepuberty** | Incomplete pubertal maturation (high pitch voice, sparse pubic + axillary hair, absence of facial hair)<br>Eunuchoidal body habitus (greater growth of extremity long bones relative to axial bones)<br>Poor muscle development, reduced peak bone mass |
| **Postpuberty** | Decrease in energy, mood, and libido<br>Fine wrinkles in corners of mouth and eyes<br>Decrease in pubic/axillary hair, hematocrit, muscle mass, strength, and BMD |

Adapted from: UpToDate, 2010; *Cecil's Essentials of Medicine*

### Treatment
- gender assignment in the newborn
- hormone replacement or supplementation
- psychological support
- gonadectomy for cryptorchidism (due to increased risk for testicular cancer)
- reduction mammoplasty for gynecomastia

# Erectile Dysfunction

- see Urology, U33



**Approach to Male Infertility**

**Infertility**: failure of a couple to conceive after 12 mo of regular intercourse without use of contraception in women <35 yr of age; after 6 mo of regular intercourse without use of contraception in women ≥35 yr

**History**
- Partner status re: infertility
- Length of time for attempt to conceive
- Prior successes with other partners
- Ejaculation problems
- Frequency of intercourse
- Prev Surg, Med Hx, STI Hx
- Hx orchitis? Cryptorchidism?
- Hx toxic exposure?
- Medications
- Alcohol and illicit drug use
- Heat exposure: bath, sauna, whirlpool
- Smoking

**P/E**
- General (height, weight, gynecomastia, masculine)
- Testicular size and consistency
- Varicocele?
- Pituitary disease?
- Thyroid disease?

**Investigations**

Should be considered for couples unable to conceive after 12 mo of unprotected and frequent intercourse. Consider earlier evaluation if suggestive medical Hx and physical, and in women ≥35 yr of age
- Semen analysis x 2 (sperm count, morphology, motility)
- Scrotal/testicular U/S (look for varicocele)
- Blood work: LH, FSH, testosterone, prolactin, thyroid function tests, DNA fragmentation of sperm, karyotype, Y chromosome deletion
- Test female partner (see Gynecology, GY22)

**Treatment**
- No specific therapy for majority of cases
- Treat specific causes
- Consider: intrauterine insemination, IVF, therapeutic donor insemination, testicular aspiration of sperm, adoption



**Pubertal Gyencomastia**
- This benign condition peaks between 13-14 years of age and spontaneously regresses in 90% of cases within 2 yr
- Waiting is often the best approach



**Causes of Gynecomastia**

**DOC TECH**
**D**rugs
**O**ther
**C**ongenital
**T**umour
**E**ndocrine
**CH**ronic disease

# Gynecomastia

## Definition
- true gynecomastia refers to benign proliferation of the glandular component of the male breast, resulting in the formation of a concentric, rubbery, firm mass extending from the nipple(s)
- pseudogynecomastia or lipomastia refers to enlargement of soft adipose tissue, especially seen in obese individuals

**Drugs Causing Gynecomastia: DISCKO**
**D**igoxin
**I-**Isoniazid
**S**pironolactone
**C**imetidine **K**etoconazole
**O**estrogen/anti-testosterone

## Etiology

### Physiologic
- puberty
- elderly
- neonatal (maternal hormone)

### Pathologic
- physiologic gynecomastia – trimodal distribution in neonatal, pubertal and older males
- drugs – spironolactone, cimetidine, ketoconazole, recombinant human GH, hCG, estrogens, antiandrogens, GnRH agonists, 5-alpha reductase inhibitors
- hormone therapy for prostate cancer
- starvation and refeeding
- male hypogonadism
- cirrhosis
- treatment of HIV infection – due to fat tissue as part of lipodystrophy
- herbal products – plant-derived oils as lavender and tea tree oil
- idiopathic
- testicular neoplasms
- CKD
- other rare causes: feminizing adrenal tumours, disorders of sex development, ectopic hCG, familial prepubertal gynecomastia
- hyperthyroidism

**Occurrence of Gynecomastia**

| 3 Peaks | % Affected |
|---|---|
| Infancy | 60-90 |
| Puberty | 4-69 |
| Ages 50-80 | 24-65 |

## Pathophysiology
- hormonal imbalance due to:
  - increased estrogen activity
    - increased production, or increased availability of estrogen precursors for peripheral conversion to estrogen
  - decreased androgen activity
    - decreased androgen production, binding of androgen to sex hormone binding globulin (SHBG), or androgen receptor blockage

## History
- recent change in breast characteristics
- pain
- trauma to testicles
- mumps
- alcohol and/or drug use
- FHx
- sexual dysfunction

## Physical Exam
- signs of feminization
- breast
  - rule out red flags suggesting breast cancer: unilateral, eccentric, hard or fixed mass, skin dimpling or retraction, and nipple discharge or crusting
  - gynecomastia occurs concentrically around nipple, is not fixed to underlying tissue
- genito-urinary exam
- stigmata of liver or thyroid disease

## Investigations
- laboratory: serum TSH, PRL, LH, FSH, testosterone, estradiol, LFTs, creatinine, hCG (if hCG is elevated, need to locate the primary tumour); however not all investigations are required for every case of gynecomastia
- CXR and CT of chest/abdomen/pelvis (to locate neoplasm)
- testicular U/S (if primary hypogonadism suspected or mass on physical examination)
- MRI of hypothalamic-pituitary region if secondary hypogonadism or pituitary adenoma suspected

## Treatment
- initial observation for most men with gynecomastia (after stopping offending medications and treating underlying cause)
- medical
  - correct the underlying disorder, discontinue responsible drug
  - androgens for hypogonadism
  - anti-estrogens: tamoxifen has most evidence for benefit
- surgical
  - longstanding (>12 mo, fibrotic), discomfort, or causing psychological distress

# Female Reproductive Endocrinology

- see Gynecology, GY22

# Paraneoplastic Syndrome

- clinical syndromes involving non-metastatic systemic effects that accompany malignant disease
- triggered by antibodies against neoplasm cross-reacting with normal tissue or by production of a physiologically active substance by the neoplasm
- commonly present with cancers of lung, breast, ovaries, or lymphatic system

**Table 39. Clinical Feature**

| Syndrome Class | Symptoms/Syndrome | Associated Malignancies | Mechanism |
|---|---|---|---|
| **Endocrine** | Cushing's syndrome | Small-cell lung cancer<br>Pancreatic carcinoma<br>Neural tumours<br>Thymoma | Ectopic ACTH and ACTH-mimicking substance secretion |
| | SIADH | Small-cell lung cancer<br>CNS malignancies | Antidiuretic hormone secretion |
| | Hypercalcemia | Lung cancer<br>Breast carcinoma<br>Renal cell carcinoma<br>Multiple myeloma<br>Ovarian carcinoma | PTH-related protein, TGF-α, TNF secretion |
| | Hypoglycemia | Hepatocellular carcinoma<br>Fibrosarcoma | Insulin or insulin-like substance secretion |
| | Carcinoid | Pancreatic carcinoma<br>Gastric carcinoma | Serotonin, bradykinin secretion |
| **Neurologic** | Lambert-Eaton myasthenic syndrome (LEMS)<br>Muscle weakness in limbs | Small-cell lung cancer | Ab interferes with ACh release |
| | Myasthenia gravis<br>Fluctuating muscle weakness and fatiguability | Thymoma | Ab interferes with ACh release |
| | Paraneoplastic limbic encephalitis<br>Depression, seizures, short-term memory loss | Small-cell lung cancer | Unknown |
| **Renal** | Hypokalemic nephropathy | Small-cell lung cancer | Ectopic ACTH and ACTH-like substance secretion |
| | Nephrotic syndrome | Lymphoma<br>Melanomas | Immunocomplex sedimentation in nephrons |
| **GI** | Watery diarrhea | Medullary thyroid carcinomas | Prostaglandin secretion |
| **Hematologic** | Erythrocytosis | Renal cell carcinoma<br>Hepatocellular carcinoma | EPO production |
| **Rheumatologic** | SLE | Lymphomas<br>Lung cancer<br>Breast carcinoma<br>Gonadal carcinoma | Anti-nuclear Ab production |
| | Scleroderma | Breast carcinoma<br>Lung cancer<br>Uterine cancer | Anti-nuclear Ab production |

## Investigations

- CBC, electrolytes, creatinine, LFTs, ALP, ESR, CRP, serum/urine electrophoresis
- serum autoantibodies, lumbar puncture
- imaging: skeletal survey, CT, MRI, PET scan
- ± endoscopy

## Treatment

- treat underlying tumour: surgery, radiation, chemotherapy
- treat immune-mediated disorder: IVIG, steroids, immunosuppressive drugs, plasmapheresis (reserved for patients with identifiable antibodies in serum)

# Diabetes Medications

| Drug Class | Mechanism of Action | Generic Drug Name | Canada Name | US Name (if different) | Dosing | Indications | Contraindications | Side Effects | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Biguanide | Sensitizes peripheral tissues to insulin → increases glucose uptake<br>Decreases hepatic glucose production by simulation of hepatic AMP-activated protein kinase (AMPK) | metformin | Glucophage®<br>Glumetza® | | 500 mg OD titrated to 2000 mg/d maximum | Useful in obese T2DM<br>Improves both fasting and postprandial hyperglycemia<br>Also ↓ TG | ABSOLUTE:<br>Moderate to severe liver dysfunction<br>Moderate renal dysfunction GFR <30 mL/min<br>Cardiac dysfunction | GI upset (abdo discomfort, bloating, diarrhea)<br>Lactic acidosis<br>Anorexia | ↓ HbA1c 1.0-1.5%<br>Weight neutral<br>Negligible risk of hypoglycemia as monotherapy |
| Insulin Secretagogue | Stimulates insulin release from β cells by causing $K^+$ channel closure → depolarization → $Ca^{2+}$ mediated insulin release<br>Use in nonobese T2DM | sulfonylureas:<br>glyburide | Diabeta®<br>Euglucon® | Micronase®<br>Glynase PreTab® | 2.5-5.0 mg/d titrated to >5 mg bid<br>Max: 20 mg/d | | ABSOLUTE:<br>Moderate to severe liver dysfunction<br>RELATIVE (glyburide and glimepiride):<br>Adjust dose in mild to moderate kidney dysfunction and avoid in severe kidney dysfunction<br>Avoid glyburide in the elderly<br>INTERACTIONS:<br>Do not combine with a non-sulfonylurea insulin secretagogue or preprandial insulin | Hypoglycemia<br>Weight gain | ↓ HbA1c 0.8%<br>Glicalazide lowest incidence of hypoglycemia |
| | | gliclazide | Diamicron®<br>Diamicron® MR | | 40-160 mg bid<br>30-120 mg OD | | | | |
| | | glimepiride | Amaryl® | | 1-8 mg OD | | | | |
| | | non-sulfonylureas:<br>repaglinide | GlucoNorm® | | 0.5-4 mg tid | Short $t_{1/2}$ of 1 h causes brief but rapid ↑ in insulin, therefore effective for postprandial control | ABSOLUTE:<br>Severe liver dysfunction<br>INTERACTIONS:<br>Do not combine with a sulfonylurea or preprandial insulin | Hypoglycemia (less than sulfonylurea)<br>Weight gain | ↓ HbA1c 0.7% for repaglinide and 0.5-1.0% for nateglinide<br>Costly<br>Must be dosed with meals |
| | | nateglinide | Starlix® | | 60-120 mg tid | | | | |
| Insulin Sensitizers (thiazolidinedione) | Sensitizes peripheral tissues to insulin → increases glucose uptake<br>Decreases FFA release from adipose<br>Binds to nuclear receptor PPAR-γ | rosiglitazone | Avandia® | | 2-8 mg OD | Rosiglitazone – indicated only in patients with T2DM for whom all other oral antidiabetic agents, in monotherapy or in combination, do not result in adequate glycemic control or are inappropriate due to contraindications or intolerance | ABSOLUTE: NYHA > class II CHF<br>INTERACTIONS: Do not combine with insulin | Peripheral edema<br>CHF<br>Anemia<br>Fluid retention and CHF<br>Increased risk of cardiac events with rosiglitazone (requires written informed consent when prescribing)<br>Increased risk of bladder cancer with pioglitazone<br>Fractures | ↓ HbA1c 0.8%<br>Delayed maximum efficacy (6-12 wk)<br>NOTE: This class of medication is rarely used anymore due to side effects and concerns about CV mortality |
| | | pioglitazone | Actos® | | 15-45 mg OD | | | | |
| α-Glucosidase Inhibitor | ↓ carbohydrate GI absorption by inhibiting brush border α-glucosidase | acarbose | Glucobay® | | 25 mg OD titrated to 100 mg tid | ↓ postprandial hyperglycemia | ABSOLUTE:<br>Inflammatory bowel disease<br>Severe liver dysfunction | Flatulence<br>Abdominal cramps<br>Diarrhea | ↓ HbA1c 0.6%<br>Not recommended as initial therapy in patients with HbA1c>8.5% |
| Dipeptidyl Peptidase-IV (DPP-IV) Inhibitor | Inhibits degradation of endogenous antihyperglycemic incretin hormones<br>Incretin hormones stimulate insulin secretion, inhibit glucagon release, and delay gastric emtyping | sitagliptan | Januvia® | | 100 mg OD | | ABSOLUTE (sitagliptin):<br>T1DM<br>DKA | Nasopharyngitis<br>URTI<br>Headache<br>Pancreatitis | ↓ HbA1c 0.7%<br>Weight neutral<br>Expensive<br>Negligible risk of hypoglycemia as monotherapy |
| | | saxagliptin | Onglyza™ | | 2.5-5 mg OD | | | | |
| | | linagliptin | Trajenta® | | 5 mg OD | | RELATIVE (sitagliptin and saxagliptin):<br>Use with dose reduction in kidney dysfunction | Stevens Johnson syndrome | |
| Glucagon-Like Peptide (GLP)-1 Analogue | Binds to GLP-1 receptor to promote insulin release<br>Insulinotropic effect suppressed as plasma glucose <4 mmol/L<br>Slows gastric emptying, suppresses inappropriately elevated glucagon levels<br>Causes β-cell regeneration and differentiation *in vitro* | exenatide | | BByetta® | 5-10 μg SC bid 1 h before meals | | ABSOLUTE:<br>T1DM<br>DKA<br>Acute pancreatitis Hx<br>RELATIVE:<br>Gastroparesis<br>ESRD<br>Personal or family history of medually thyroid cancer (MTC) | N/V, diarrhea<br>Dizziness, headache<br>Muscle weakness<br>Anti-exenatide antibodies<br>Pancreatitis | ↓ HbA1c 1.0%<br>Weight loss<br>Negligible risk of hypoglycemia as monotherapy |
| | | liraglutide | | Victoza® | 0.6-1.8 mg OD SC | | | | |
| | | semaglutide | | Ozempic® | | | | | |
| | | dulaglutide | | Trulicity® | | | | | |

# Diabetes Medications (continued)

| Drug Class | Mechanism of Action | Generic Drug Name | Canada Name | US Name (if different) | Dosing | Indications | Contraindications | Side Effects | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Sodium-glucose linked transporter 2 (SGLT2) Inhibitor | Enhances urinary glucose excretion by inhibiting glucose reabsorption in the proximal renal tubule | canagliflozin | Invokana® | | 100 mg OD before first meal of the day | | ABSOLUTE:<br>Severe renal impairment<br>ESRD<br>Patients on dialysis | UTI, genital infections<br>Hypotension caution with concomitant loop diuretic use<br>Caution with renal dysfunction<br>Hyperlipidemia (raises LDL and HDL)<br>Dapagliflozin not to be used in patients with active or history of bladder cancer<br>Rare diabetic ketoacidosis (may occur with no hyperglycemia) | ↓ HbA1c 0.7-1.0%<br><br>Negligible risk of hypoglycemia as monotherapy<br><br>Cause weight loss |
| | | dapagliflozin | Forxiga® | | 5 mg OD in the morning with or without food | | | | |
| | | empagliflozin | Jardiance® | | 10 mg OD in the morning with or without food | | | | |

# Dyslipidemia Medications

| Drug Class | Mechanism of Action | Generic Drug Name | Canada Name | US Name (if different) | Dosing | Indications | Contraindications | Side Effects |
|---|---|---|---|---|---|---|---|---|
| HMG-CoA Reductase Inhibitor (statins) | Inhibits cholesterol biosynthesis, ↓ LDL synthesis, ↑ LDL clearance, modest ↑ HDL, limited ↓ VLDL | atorvastatin<br>fluvastatin<br>lovastatin<br>pravastatin<br>rosuvastatin<br>simvastatin | Lipitor®<br>Lescol®<br>Mevacor®<br>Pravachol®<br>Crestor®<br>Zocor® | | 10-80 mg/d<br>20-80 mg/d<br>20-80 mg/d<br>10-40 mg/d<br>5-40 mg/d<br>10-80 mg/d | 1st line monotherapy<br>Used for ↑ LDL, ↑ TG | Active liver disease | ↑ liver enzymes<br>Myositis (↑ risk if combined with fibrates)<br>Rhabdomyolysis |
| Fibrates | Activate PPAR α, upregulate lipoprotein lipase + apo A1, ↓ VLDL, ↓ TG, modest ↓ LDL, modest ↑HDL | bezafibrate<br>fenofibrate<br>gemfibrozil | Bezalip®<br>Lipidil®<br>Lopid® | | 400 mg/d<br>48-200 mg/d<br>600-1200 mg/d | Used for ↑ TG, hyperchylomicronemia | Hepatic disease<br>Renal disease | GI upset<br>Skin rashes<br>↑ risk of gallstone formation<br>↑ risk of rhabdomyolysis when combined with statins |
| Niacin | Inhibits secretion of hepatic VLDL via lipoprotein lipase (LPL) pathway → decreased VLDL and LDL; decreased clearance of HDL | nicotinic acid | Niaspan®<br>generic niacin | Niacor® | 0.5-2 g/d | Used for severe hypertriglyceridemia not controlled by fibrate | Hypersensitivity<br>Hepatic dysfunction<br>Active PUD<br>Hyperuricemia<br>Severe hypotension | Generalized flushing<br>Abnormal liver enzymes<br>Pruritus<br>IGT<br>Watch glucose control with overt DM |
| Bile Acid Sequestrants | Resins that bind bile acids in intestinal lumen and prevent absorption thereby<br>↓ LDL | cholestyramine | Questran® | | 2-24 g/d | Used for ↑ LDL<br>Use as adjunct with statins or fibrates | Complete biliary obstruction<br>TG >3.5 mmol/L | Constipation, nausea<br>Flatulence<br>Bloating<br>Rise in TG<br>Binds other medications |
| | | colestipol | Colestid® | | 5-30 g/d | | | |
| Cholesterol Absorption Inhibitors | Inhibits cholesterol absorption at the small intestine brush border | ezetimibe | Ezetrol® | Zetia® | 10 mg/d | Used for ↑ LDL | Hypersensitivity<br>Hepatic dysfunction (when used with statin)<br>Do not combine with fibrates or bile acid resins | Fatigue<br>Pharyngitis<br>Sinusitis<br>Abdominal pain<br>Diarrhea<br>Arthralgia |
| Anti-PCSK9 | Inhibits degradation of the LDL receptor by PCSK9 enzyme<br>LDL clearance | evolocumab | Repatha® | | 140 mg q2w or 420 mg qmon | Add-on to maximally tolerated statin therapy in heterozygous FH (evolocumab, alirocumab) and homozygous FH (evolocumab)<br>Consider in patients with atherosclerotic CVD and LDL-C not at target despite maximally tolerated statin ± ezetimibe | Hypersensitivity<br>No studies regarding use in severe hepatic or renal impairment | Nasopharyngitis, URTI, influenza<br>Sinusitis<br>Back pain<br>Myalgia<br>Arthralgia<br>Nausea |
| | | alirocumab | Praluent® | | 75 mg q2w or 300 mg qmo | | | |

# Thyroid Medications

| Drug Class | Mechanism of Action | Generic Drug Name | Canada Name | US Name (if different) | Dosing | Indications | Contraindications | Side Effects |
|---|---|---|---|---|---|---|---|---|
| Antithyroid Agent (thionamides) | Decreases thyroid hormone production by inhibiting iodine and peroxidase from interacting with thyroglobulin to form $T_4$ and $T_3$<br>PTU also interferes with conversion of $T_4$ to $T_3$ | propylthiouracil (PTU) | Propyl-Thyracil® | | Start 100 mg PO tid, then adjust accordingly<br>Thyroid storm: start 150-300 PO qid, then adjust accordingly | Hyperthyroidism, thyroid storm | Hypersensitivity<br>PTU recommended in 1st trimester, MMI during 2nd and 3rd trimester<br>Lactation: safe with PTU <300 mg/d and MMI <20-30 mg/d | N/V<br>Rash<br>Drug-induced hepatitis<br>Agranulocytosis<br>Hepatitis with PTU<br>Cholestasis with MMI |
| | | methimazole (MMI) | Tapazole® | | Start 5-20 mg PO OD, then adjust accordingly<br>Up to 60 mg OD may be required | | | |
| Thyroid Hormone | Synthetic form of thyroxine ($T_4$) | levothyroxine<br>l-thyroxine | Synthroid®<br>Eltroxin® | Levoxyl® | 0.05-2.0 mg/d, usually 1.6x weight (kg) is dose in micrograms<br>In elderly patients start at 0.025 mg/d | Hypothyroidism<br>Post thyroidectomy | Recent MI, thyrotoxicosis | If wrong dosing: symptoms of hypothyroidism or hyperthyroidism<br>Skin rash from dye in pill |
| Antithyroid Agent Radiopharmaceutical | Radioactive isotope of iodine that is incorporated into the thyroid gland irradiating the area and destroying local glandular tissue | sodium iodide I-131 | Iodotope® | | Dose corrected for 24 h radioactive iodine uptake<br>Hyperthyroidism 4-12 mCi<br>Thyroid Ca 50-150 mCi | Hyperthyroidism<br>Thyroid malignancy | Hypersensitivity<br>Concurrent antithyroid medication<br>Pregnancy, lactation | N/V<br>Bone marrow suppression<br>Sialadenitis<br>Thyroiditis |

# Metabolic Bone Disease Medications

| Drug Class | Mechanism of Action | Generic Drug Name | Canada Name | US Name (if different) | Dosing | Indications | Contraindications | Side Effects |
|---|---|---|---|---|---|---|---|---|
| Bisphosphonates | Inhibits osteoclast-mediated bone resorption | alendronate | Fosamax® | | Osteoporosis:<br>5-10 mg OD<br>70 mg once weekly<br>Paget's<br>40 mg OD for 6 mo | Prevention of postmenopausal osteoporosis<br>Treatment of osteoporosis<br>Glucocorticoid-induced osteoporosis<br>Paget's disease | Esophageal stricture or achalasia (oral)<br>Unable to stand or sit upright for >30 min (oral)<br>Hypersensitivity<br>Hypocalcemia<br>Renal insufficiency (CrCl <35 mL/min)<br>History or atypical femoral fracture or osteonecrosis of the jaw | GI<br>MSK pain<br>Headache<br>Osteonecrosis of the jaw<br>Atypical femoral fracture |
| | | risedronate | Actonel® | | Osteoporosis:<br>5 mg OD<br>35 mg once weekly<br>150 mg once monthly<br>Paget's:<br>30 mg OD for 2 mo | Treatment and prevention of postmenopausal osteoporosis<br>Treatment and prevention of glucocorticoid-induced osteoporosis<br>Paget's disease | | |
| | | pamidronate | Aredia® | | Hypercalcemia of malignancy<br>60-90 mg IV over 2-24 h<br>Wait at least 7 d before considering retreatment | Hypercalcemia of malignancy<br>Paget's disease<br>Osteolytic bone metastases of breast cancer<br>Osteolytic lesions of multiple myeloma | | |
| | | zoledronate | Zometa®<br>Aclasta® | | 5 mg IV once yearly<br>5 mg IV | Treatment of osteoporosis<br>Hypercalcemia of malignancy<br>Treatment and prevention of skeletal complications related to cancer | | |
| Selective Estrogen Receptor Modulators | Decreases resorption of bone through binding to estrogen receptors | raloxifene | Evista® | | 60 mg OD | Treatment and prevention of postmenopausal osteoporosis (2nd line) | Lactation<br>Pregnancy<br>Active or past history of DVT, PE, or retinal vein thrombosis | Hot flashes<br>Leg cramps<br>Increased risk of fatal stroke, venous thromboembolism |

# Metabolic Bone Disease Medications (continued)

| Drug Class | Mechanism of Action | Generic Drug Name | Canada Name | US Name (if different) | Dosing | Indications | Contraindications | Side Effects |
|---|---|---|---|---|---|---|---|---|
| Calcitonin | Inhibits osteoclast-mediated bone resorption | calcitonin | Miacalcin® | | One spray (200 IU) per d, alternating nostrils | Treatment for postmenopausal osteoporosis (greater than 5 yr postmenopause) | Clinical allergy to salmon-calcitonin | Rhinitis<br>Epistaxis<br>Sinusitis<br>Nasal dryness |
| Anti-RANKL Monoclonal Ab | Inhibits RANKL (osteoclast differentiating factor) → inhibits osteoclast formation and decreases bone resorption | denosumab | Prolia™ | Xgeva™ | 60 mg SC q6mo | Treatment for postmenopausal women at high risk of fracture<br>Prevent skeletal-related events in patients with bone metastasis from solid tumours<br>Also approved for glucocorticoid-induced osteoporosis, and for men | Hypocalcemia<br>Vitamin D insufficiency | Fatigue/headache/GI injection site reaction<br>Hypocalcemia<br>Atypical femoral fracture<br>Osteonecrosis of the Jaw |
| PTH | Stimulates new bone formation by preferential stimulation of osteoblastic activity over osteoclastic activity | teriparatide | Forteo® | | 20 µg SC OD x 18-24 mo | Treatment for postmenopausal women with osteoporosis who are at high risk for fracture<br>Treatment for men with primary or hypogonadal osteoporosis who are at high risk for fracture<br>Also approved for Glucocorticoid-induced osteoporosis | Paget's disease<br>Prior external beam or implant radiation therapy involving the skeleton<br>Bone metastases<br>Metabolic bone diseases other than osteoporosis | Orthostatic hypotension<br>Hypercalcemia<br>Dizziness<br>Leg cramps |
| Calcium | Inhibits PTH secretion | | | | 1200 mg/d (including diet)<br>Divided in 3 doses | Osteopenia<br>Osteoporosis<br>Prevention of metabolic bone disease | Caution with renal stones | Vomiting<br>Constipation<br>Dry mouth |
| Vitamin D | Regulation of calcium and phosphate homeostasis | cholecalciferol (vitamin D3) | | | 800 -2000 IU/d (higher doses required in Insufficiency or deficiency) | Osteopenia<br>Osteoporosis<br>Prevention of metabolic bone disease | Caution in patients on digoxin (risk of hypercalcemia which may precipitate arrhythmia) | Hypercalcemia<br>Headache<br>Nausea and vomiting<br>Constipation |
| | | ergocalciferol (vitamin D2) | Drisdol®<br>Erdol® | | 50,000 IU/wk | Osteoporosis in patients with liver dysfunction, refractory rickets, hypoparathyroidism | Hypercalcemia<br>Malabsorption syndrome<br>Decreased renal function | |
| | | calcitriol ($1,25(OH)_2$-D) | Rocaltrol® | | Start 0.25 µg/d<br>Titrate up by 0.25 µg/d at 4-8 wk intervals to 0.5-1 µg/d | Hypocalcemia and osteodystrophy in patients with chronic renal failure on dialysis<br>Hypoparathyroidism | Hypercalcemia<br>Vitamin D toxicity | |
| | | | Calcijex® | | Start 0.25 µg/d<br>Titrate up by 0.25 µg/d at 2-4 wk intervals to 0.5-2 µg/d | | | |

# Adrenal Medications

| Drug Class | Mineralocorticoid Activity | Generic Drug Name | Potency Relative to Cortisol) | Equivalent Dose (mg) | Duration of Action ($t_{1/2}$ in h) | Dosing | Comments |
|---|---|---|---|---|---|---|---|
| Hydrocortisone | Yes | cortef<br>solu-Cortef | 1.0 | 20 | 8 | Adrenal Crisis: 50-100 mg IV bolus, then 50-100 mg q8h (continuous infusion x 24-48 h)<br>PO once stable (50 mg q8h x 48 h, then taper over 14 d)<br>Chronic AI: 15-20 mg PO OD (2/3 AM, 1/3 PM) | In high doses, mineralocorticoid side effects may emerge (salt + water retention, ECF volume expansion, HTN, low $K^+$ metabolic alkalosis) |
| Cortisone Acetate | Yes | cortisone acetate | 0.8 | 25 | oral = 8<br>IM = 18+ | Adrenal Crisis: 75-300 mg/d PO/IM divided q12-24h<br>Chronic AI: 25 mg/d | Pro-drug which is converted to active form as hydrocortisone<br>High doses can result in mineralocorticoid side effects (see above) |
| **Mineralocorticoid** | | | | | | | |
| Fludrocortisone | 100% | — | — | | | Chronic: 0.1 mg daily | Replaces aldosterone in primary adrenal insufficiency |
| Prednisone | No | prednisone | 4 | 5 | 16-36 | Adrenal Crisis: 15-60 mg/d PO qd or divided bid/qid<br>Chronic AI: 5 mg daily | Pro-drug which is converted to active form as prednisolone |
| Dexamethasone | No | dexamethasone | 30 | 0.7 | 36-54 | Adrenal Crisis: 4 mg IV; repeat q2-6h if necessary | Used for undiagnosed adrenal insufficiency (does not interfere with measurement of serum cortisol levels) |

# Landmark Endocrinology Trials

| Trial | Reference | Results |
|---|---|---|
| **DIABETES** | | |
| ACCORD | NEJM 2008;358:2560-72 | Compared with standard therapy the use of intensive therapy to target normal HbA1c levels (<6%) for 3.5 yr increased mortality and did not significantly reduce major cardiovascular events |
| ADVANCE | NEJM 2008;358:2545-59 | Intensive glucose control that lowered the HbA1c value to 6.5% and reduced the incidence of nephropathy but did not significantly reduce major macrovascular events, death from cardiovascular events, or death from any cause; hypoglycemia was more common in the intensive control group |
| BARI-2D | NEJM 2009;360:2503-15 | In patients with both T2DM and CAD, no significant difference was found in the rates of death and major cardiovascular events in patients undergoing prompt revascularization and those undergoing medical therapy or between strategies of insulin sensitization and insulin |
| DCCT | NEJM 1993;329:977-86 | Intensive blood glucose control delayed the onset and reduced the progression of microvascular complications (retinopathy, nephropathy, and neuropathy) in T1DM |
| EDIC | NEJM 2005;353:2644-53 | Compared with conventional therapy, intensive DM therapy early on without macrovascular disease (goal HbA1c <6.05%) has long-term beneficial effects on the risk of cardiovascular disease in patients with T1DM |
| Look AHEAD | NEJM 2013;369:145-54 | Moderate weight loss (<7% BW) and increased exercise are not associated with reduction in CVD and its complications among overweight or obese patients with T2DM |
| NAVIGATOR | NEJM 2010;362:1463-90 | In patients with impaired glucose tolerance, nateglinide did not reduce progression to DM or risk of cardiovascular events while valsartan only reduced progression to DM |
| PREDIMED | NEJM 2013;368:1279-90 | A Mediterranean diet with extra-virgin olive oil or nuts reduces rates of MI, CVA, or CV death in those at high risk for CV disease (outcome was driven by reduction in rates of CVA) |
| Steno-2 | NEJM 2008;358:580-91 | In at-risk patients with T2DM, intensive intervention with multiple drug combinations and behaviour modification had sustained significant beneficial effects with respect to vascular complications and mortality; multifactorial intervention is critical in the management of T2DM |
| UKPDS | Lancet 1998;352:837-53 | Intensive blood glucose control reduces microvascular but not macrovascular complications in T2DM |
| UKPDS Extension | NEJM 2008;359:1577-89 | Continued risk reduction in microvascular risk and emergent risk reductions for MI and death from any cause 10 yr post UKPDS trial follow-up in T2DM |
| VADT | NEJM 2009;360:1-11 | In patients with longstanding poorly controlled T2DM, intensive glucose control had no significant effect on the rates of major cardiovascular events, death, or microvascular complications; adverse events, predominantly hypoglycemia, were more common in the intensive control group |
| **LIPIDS** | | |
| 4S | Lancet 1994;344:1383-89 | In patients with angina or previous MI and high total cholesterol, simvastatin reduced: all-cause mortality, fatal and nonfatal coronary events, and need for coronary artery bypass surgery or angioplasty |
| FIELD | Lancet 2005;366:1849-61 | In patients with T2DM not previously on statin therapy, fenofibrate did not significantly reduce the risk of the primary outcome of coronary events; it did reduce non-fatal MI and revascularizations |
| HPS | Lancet 2002;360:7-22 | In high-risk patients with various cholesterol values, simvastatin reduced all-cause mortality, coronary deaths, and major vascular events |
| Jupiter | NEJM 2008;359:2195-207 | Rosuvastatin significantly reduced the incidence of major cardiovascular events in patients with elevated high-sensitivity CRP levels and no hyperlipidemia |
| TNT | NEJM 2005;352:1425-35 | Lipid-lowering therapy with atorvastatin 80 mg/d in patients with stable CHD provides clinical benefit beyond atorvastatin 10 mg/d |

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Notes

# FM Family Medicine

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# Acronyms

| | |
|---|---|
| ABG | arterial blood gas |
| ABPM | amubulatory blood pressure measurement |
| ACR | albumin:creatinine ratio |
| ACEI | angiotensin converting enzyme inhibitors |
| AIN | anal intraepithelial neoplasia |
| AKI | acute kidney injury |
| AMC | another medical condition |
| AOBP | automated office blood pressure |
| AR | absolute reduction |
| ARB | angiotensin receptor blockers |
| BMI | body mass index |
| BPH | benign prostatic hyperplasia |
| BPPV | benign paroxysmal positional vertigo |
| BRBPR | bright red blood per rectum |
| C&S | culture and sensitivity |
| CA | cancer |
| CABG | coronary artery bypass graft |
| CAD | coronary artery disease |
| CBC | complete blood count |
| CBT | cognitive behavioural therapy |
| CCB | calcium channel blockers |
| CF | cystic fibrosis |
| CHEP | Canadian Hypertension Education Program |
| CHF | congestive heart failure |
| CK | creatine kinase |
| CNS | central nervous system |
| CPAP | continuous positive airway pressure |
| CRC | colorectal cancer |
| CT | computed tomography |
| CV | cardiovascular |
| CVA | costovertebral angle |
| CVD | cardiovascular disease |
| DHP | dihydropyridine |
| DKA | diabetic ketoacidosis |
| DM | diabetes mellitus |
| DMPA | depot medroxyprogesterone |
| DRE | digital rectal exam |
| DS | double strength |
| EC | emergency contraception |
| ED | emergency department |
| ER | extended release |
| F/U | follow-up |
| FAP | familial adenomatous polyposis |
| FBG | fasting blood glucose |
| FIT | fecal immunochemical testing |
| FOBT | fecal occult blood test |
| FRS | Framingham Risk Score |
| GAD | generalized anxiety disorder |
| GERD | gastroesophageal reflux disease |
| GI | gastrointestinal |
| HAART | highly active anti-retroviral therapy |
| HDL-C | high density lipoprotein cholesterol |
| HEENT | head, ears, eyes, nose, and throat |
| HNPCC | hereditary non polyposis colon cancer |
| hs-CRP | high sensitivity C-reactive protein |
| HSIL | high-grade squamous intraepithelial lesion |
| HPV | human papillomavirus |
| HRT | hormone replacement therapy |
| IBD | inflammatory bowel disease |
| IBS | irritable bowel syndrome |
| ICS | inhaled corticosteroids |
| IFG | impaired fasting glucose |
| IGT | impaired glucose tolerance |
| IHD | ischemic heart disease |
| INH | isoniazid |
| IPT | interpersonal therapy |
| IVP | intravenous pyelogram |
| KUB | kidneys, ureter, bladder x-ray |
| LDL-C | low density lipoprotein cholesterol |
| LMWH | low molecular weight heparin |
| LSIL | low-grade squamous intraepithelial lesion |
| LV | left ventricle |
| LVH | left ventricle hypertrophy |
| MDI | metered dose inhaler |
| MAOI | monoamine oxidase inhibitor |
| MMSE | mini mental status examination |
| MOCA | Montreal cognitive assessment |
| MS | multiple sclerosis |
| MSM | men who have sex with men |
| MUFA | monounsaturated fatty acids |
| N/V | nausea and vomiting |
| NPH | human insulin isophane |
| NTD | neural tube defects |
| NTG | nitroglycerin |
| O&P | ova and parasites |
| OA | osteoarthritis |
| OBPM | office blood pressure measurement |
| OCD | obsessive compulsive disorder |
| OCP | oral contraceptive pill |
| OCPD | obsessive compulsive personality disorder |
| OD | once a day |
| OGTT | oral glucose tolerance test |
| OSA | obstructive sleep apnea |
| OTC | over the counter |
| PCOS | polycystic ovarian syndrome |
| PFT | pulmonary function test |
| PHE | periodic health examination |
| PID | pelvic inflammatory disease |
| PMS | premenstrual syndrome |
| PND | paroxysmal nocturnal dyspnea |
| PPI | proton pump inhibitor |
| PPD | purified protein derivative |
| PSA | prostate specific antigen |
| PTSD | post-traumatic stress disorder |
| PUD | peptic ulcer disease |
| PUFA | polyunsaturated fatty acids |
| PVD | peripheral vascular disease |
| R&M | routine + microscopic |
| RA | rheumatoid arthritis |
| RCT | randomized controlled trial |
| ROM | range of motion |
| RSV | respiratory syncytial virus |
| SAH | subarachnoid hemorrhage |
| SDRI | serotonin dopamine reuptake inhibitor |
| SIDS | sudden infant death syndrome |
| SLE | systemic lupus erythematosis |
| SNRI | serotonin norepinephrine reuptake inhibitor |
| SOB | shortness of breath |
| SSRI | selective serotonin reuptake inhibitor |
| TB | tuberculosis |
| TC | total cholesterol |
| TCA | tricyclic antidepressant |
| TG | triglyceride |
| TIA | transient ischemic attack |
| TM | tympanic membrane |
| TMJ | temporomandibular joint |
| TUIP | transurethral incision of the prostate |
| TURP | transurethral resection of the prostate |
| UC | ulcerative colitis |
| URTI | upper respiratory tract infection |
| UTI | urinary tract infection |
| VAIN | vaginal intraepithelial neoplasia |
| VDRL | venereal disease research laboratory |
| VIN | vulvar intraepithelial neoplasia |
| VBI | vertebrobasilar insufficiency |
| WSIB | Workplace Safety and Insurance Board |

# Four Principles of Family Medicine

**College of Family Physicians of Canada**

**1. The family physician is a skilled clinician**
- diagnoses and manages diseases common to the population served
- recognizes importance of early diagnosis of serious life-threatening illnesses

**2. Family medicine is a community-based discipline**
- provides information and access to community services
- responds/adapts to changing needs and circumstances of the community

**3. The family physician is a resource to a defined practice population**
- serves as a health resource
- advocates for public policy to promote health

**4. The patient-physician relationship is central to the role of the family physician**
- commits to the person, not just the disease
- promotes continuity of patient care

# Periodic Health Examination

- Canadian Task Force on Preventive Health Care established in 1976 to develop and disseminate clinical practice guidelines for primary and preventive care
- recommendations are based on systematic analysis of scientific evidence
- periodic preventive health visits are recommended instead of annual physical examinations

**Adult Periodic Health Exam**
Male and female evidence-based preventive care checklist forms are available online at http://www.cfpc.ca, most recently updated in 2015

## Purpose of the Periodic Health Examination

- primary prevention: identify risk factors for common diseases; counsel patients to promote healthy behaviour
- secondary prevention: pre-symptomatic detection of disease to allow early treatment and to prevent disease progression

## Classification of Recommendations (GRADE, 2011)

**Strength of Recommendation**
- **strong**: confidence that desirable effects outweigh undesirable effects (strong recommendation for an intervention) or that the undesirable effects outweigh desirable effects (strong recommendation against an intervention)
  - implies that most individuals will be best served by the recommended course of action

- **conditional**: desirable effects probably outweigh the undesirable effects (conditional recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (conditional recommendation against an intervention)
  - implies that most people would want the recommended course of action but that many would not
  - different choices will be appropriate for different individuals, patients require support in reaching a management decision consistent with his/her values and preferences

### Quality of Evidence

- high: high level of confidence that true effect lies close to the estimate of the effect
- moderate: true effect likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- low or very low: true effect may be substantially different from the estimate of the effect

**Table 1. Periodic Health Exam**

| | General Population | Special Population |
|---|---|---|
| **Discussion** | Dental hygiene (community fluoridation, brushing, flossing) (A)<br>Noise control and hearing protection (A)<br>Screen for poverty<br>Smokers: counsel on smoking cessation, provide:<br>Nicotine replacement therapy (A)<br>Referral to smoking cessation program (B)<br>Dietary advice on leafy green vegetables and fruits (B)<br>Seat belt use (B)<br>Injury prevention (bicycle helmets, smoke detectors) (B)<br>Moderate physical activity (B)<br>Avoid sun exposure and wear protective clothing (B)<br>Problem drinking screening and counselling (B)<br>Counselling to protect against STIs (B)<br>Nutritional counselling, dietary advice on fat, and cholesterol (B)<br>Dietary advice on calcium and vitamin D requirements (B) | **Pediatrics:** Home visits for high risk families (A), Inquiry into developmental milestones (B)<br><br>**Adolescents**: Counsel on sexual activity and contraceptive methods (B), Counsel to prevent smoking initiation and substance use (B)<br><br>**Perimenopausal Women (>50):** Assess for risk factors for: osteoporosis and fracture (A), Counsel on osteoporosis, Counsel on risks/benefits of hormone replacement therapy (B)<br><br>**Adults >65**: Follow-up on caregiver concern of cognitive impairment (A), Multidisciplinary post-fall assessment (A) |
| **Physical** | Blood pressure measurement, using techniques described in CHEP guidelines (strong recommendation; moderate quality evidence)<br>BMI measurement in obese adults (B) | **Pediatrics:** Repeated examinations of hips, eyes, and hearing (especially in first year of life) (A), Serial height, weight, and head circumference (B), Visual acuity testing after age 2 (B)<br><br>**Adults >65:** Visual acuity (Snellen sight chart) (B), Hearing impairment (inquiry, whispered voice test, audioscope) (B)<br><br>**First-Degree Relative with Melanoma:** Full body skin exam (B) |
| **Tests** | See recommendations below for age and gender specific screening for diabetes, dyslipidemia, hypertension, and cancer screening (colon, prostate, cervical, lung, and breast) | **Pediatrics:** Routine hemoglobin for high risk infants (B), Blood lead screening of high risk infants (B)<br><br>**TB High Risk Groups**: Mantoux skin testing (A)<br><br>**STI High Risk Groups**: Voluntary HIV antibody screening (A), Gonorrhea screening (A), Chlamydia screening in women (B), Syphillis screening (A)<br><br>**Syphilis Risk Group**: VDRL test (A) |
| **Therapy** | Folic acid supplementation to women of child-bearing age (A)<br>Pharmacologic treatment of HTN (Refer to CHEP Guidelines) (A)<br>Varicella vaccine for children age 1-12 and susceptible adolescents/adults (A)<br>Rubella vaccine for all non-pregnant women of child-bearing age unless there is proof of immunity via immunization records or serology (B)<br>Tetanus vaccine: routine booster q10yr if had 1° series (A)<br>Pertussis vaccine: adults <65 should receive one booster given as Tdap– Adacel® or Boostrix® (A)<br>Herpes zoster vaccine for adults ≥60 | **Pediatrics:** Routine immunizations (A), Hepatitis B, HPV, and Meningococcal immunizations are offered in schools in most Canadian provinces<br><br>**Influenza High Risk Groups**: Outreach strategies for vaccination (A), Annual immunization (B), now recommended for all<br><br>**TB High Risk Groups** INH prophylaxis for household contacts or skin test converters (B), INH prophylaxis for high risk sub-groups (B)<br><br>**Immunocompromised/Age≥65/COPD/Asthma/CHF/Asplenia/Liver Disease/Renal Failure/DM:**<br>Pneumococcal vaccine (Pneumovax®) (A) |

Classification of recommendation in brackets: A - High quality of evidence; B – Moderate quality of evidence. See www.canadiantaskforce.ca – for up-to-date guidelines Reference: Canadian Task Force on Preventive Health Care, 2014

**Choosing Wisely Canada**
http://www.choosingwiselycanada.org/
A campaign to help clinicians and patients engage in conversations about unnecessary tests and treatments and make smart and effective choices to ensure high quality care

**Folic Acid Supplementation in Pregnancy (Joint SOGC-Motherisk Clinical Guideline May 2015)**

- To prevent neural tube defects in all women capable of becoming pregnant
- Low risk women (no personal health risks, planned pregnancy): diet of folate-rich foods and a daily oral multivitamin supplement containing 0.4-1.0 mg folic acid for at least 2-3 mo before conception, throughout pregnancy, and 4 to 6 wk postpartum or as long as breast-feeding continues
- High risk women (health risks including epilepsy, insulin-dependent diabetes, BMI >35, family history of NTD, high risk ethnic group): diet of folate-rich foods and daily supplementation with multivitamins with 5 mg folic acid at least 3 mo prior to conception until 12 wk post conception
- From wk 12 post-conception until postpartum period (4-6 wk or as long as breastfeeding continues): 0.4-1.0 mg of folic acid supplementation is sufficient
- Women with additional lifestyle issues (poor compliance with medications, no consistent birth control, taking possible teratogenic substances): higher folic acid dose of 5 mg and counselling about prevention of birth defects

# Breast Cancer Screening Guidelines

### 2018 Canadian Task Force on Preventive Health Care

- average-risk women: women age 40-74 with no personal history of breast cancer, history of breast cancer in 1st degree relatives, known mutations of the *BRCA1/BRCA2* genes or previous exposures of the chest wall to radiation

### Mammography
- age 40-49: recommend not screening with mammography (conditional recommendation, low-certainty evidence)
- age 50-74: recommend routine screening q2-3yr (conditional recommendation, very low-certainty evidence)
- age 75+: screen if benefits outweigh harm, must take overall health into account

### Magnetic Resonance Imaging and Ultrasound
- recommend not using MRI, tomosynthesis or ultrasound to screen for breast cancer in women not at increased risk (strong recommendation, no evidence)

### Clinical Breast Examination
- recommend not performing CBE to screen for breast cancer (conditional recommendation, no evidence)

## Breast Self-Examination

- recommend against routine breast self-examination to screen for breast cancer (conditional recommendation, low-certainty evidence)
- for more information on benign breast lesions and breast cancer, see General Surgery, GS60

## Lung Cancer Screening Guidelines

### 2016 Canadian Task Force on Preventive Health Care
- apply to adults aged 18 and older who are not suspected of having lung cancer
- recommend low dose CT scan for annual screening in adults aged 55-74 with at least a 30 pack-yr smoking history who currently smoke or quit less than 15 yr ago, up to three consecutive times
- chest x-ray is not recommended to screen for lung cancer, with or without sputum cytology

## Colorectal Cancer Screening Guidelines

### 2016 Canadian Task Force on Preventive Health Care
- apply to average risk individuals (asymptomatic, no family history of UC, polyps, or CRC)
- average risk testing should begin at age 50, but assessment for risk factors should begin earlier to identify high-risk individuals 50-59 (conditional recommendation, moderate quality evidence), 60-74 (strong recommendation, moderate quality evidence)
- recommend screening with FOBT (either high sensitivity FOBT or FIT) q2yr OR flexible sigmoidoscopy q10yr
- colonoscopy not recommended as a screening test
- screening is not recommended after age 75, but it may be assessed on an individual basis for ages 76-85
- for more information on colorectal neoplasms, see General Surgery, GS38

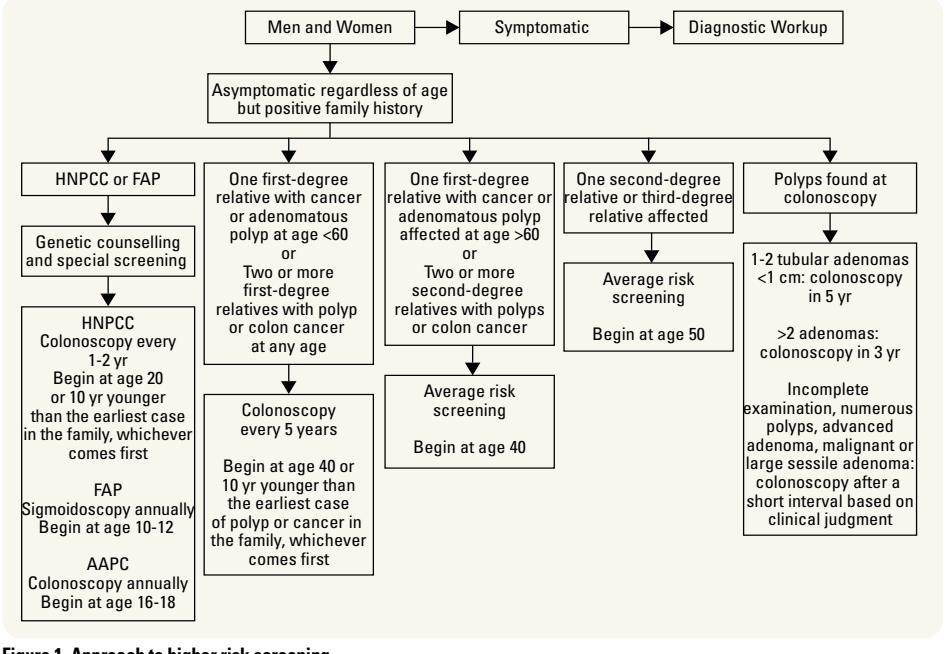



**Figure 1. Approach to higher risk screening**
AAPC = attenuated adenomatous polyposis; FAP = familial adenomatous polyposis; HNPCC = hereditary nonpolyposis colorectal cancer; 1st degree relatives: parents, siblings, children; 2nd degree relatives: grandparents, aunts, uncles; 3rd degree relatives: great grandparents or cousins. Figure printed with permission from Can J Gastroenterol 2004;18:93-99. Also see: Colorectal Screening for Cancer Prevention in Asymptomatic Patients, March 2013. Available from http://www.bcguidelines.ca/pdf/colorectal_screening.pdf

# Cervical Cancer Screening Guidelines

- either conventional Papanicolaou (Pap) smear or liquid based cytology testing
- endocervical and exocervical cell sampling (aim is to sample the transitional zone)
- best identifies squamous cell abnormalities, less reliable for glandular abnormalities
  - false positives 5-10%, false negatives 10-40% (for single test)
  - false negative rate 50% for existing cervical cancer
- cervical cancer screening guidelines differ by provincial jurisdiction (see The Society of Obstetricians and Gynaecologists of Canada guidelines)

### 2013 Canadian Task Force for Preventive Care Guidelines

- recommend screening all women age ≥25 q3yr who are or have ever been sexually active (includes intercourse or digital/oral activity with partner of either sex); age 25-29 (conditional recommendation; moderate quality evidence), age 30-69 (strong recommendation; high quality evidence)
- can reccomdend discontinuing screening in women age ≥70: if 3 normal tests in a row and no abnormal tests in last 10 yr, (conditional recommendation; low quality evidence)
- **Ontario guidelines**
  - screen all women age ≥21 who are or have ever been sexually active
  - if cytology is normal, can screen every 3 yr
  - women age ≥70: if 3 successive negative Pap tests in last 10 yr, can discontinue screening
  - women who are not sexually active by age 21 should delay cervical cancer screening until sexually active
- pregnant women and women who have sex with women should follow the routine cervical screening regimen
- women who have had a hysterectomy
  - total: discontinue screening if hysterectomy was for benign disease and no history of cervical dysplasia or HPV infection, continue to swab vaginal vault if history of uterine malignancy/dysplasia
  - subtotal: continue screening according to guidelines
- exceptions to guidelines
  - immunocompromised (transplant, steroids, diethylstilbestrol exposure, HIV)
  - previously unscreened patients
- for more information on cervical cancer (see Gynecology, GY43)

**Prostate Cancer Mortality at 11 Years of Follow-Up**
NEJM 2012;366:981-990
**Purpose**: To evaluate the effect of prostate-specific antigen (PSA) testing on prostate cancer mortality.
**Methods**: Update of European Randomized Study of Screening for Prostate Cancer with two additional years of follow-up. Men between the ages of 50 and 74 yr were eligible, and eight European countries were involved. Men were randomly assigned to screening or control. Primary outcome was prostate cancer-related mortality.
**Results**: 162,388 men were involved, and a median follow-up of 11 yr was completed. Relative reduction in the risk of prostate cancer-related deaths was 21% in favour of the screening group (rate ratio (RR) 0.79, 95% CI 0.68-0.91, p=0.001), and absolute reduction was 0.10 deaths/1000 person-years (1.07 deaths/1000 randomized men). 1055 men would need to be invited for screening to prevent one death from prostate cancer with 11 yr follow-up. No significant between-group difference in all-cause mortality was noted.
**Conclusion**: PSA-based screening significantly reduced prostate cancer-related mortality but did not affect all-cause mortality.

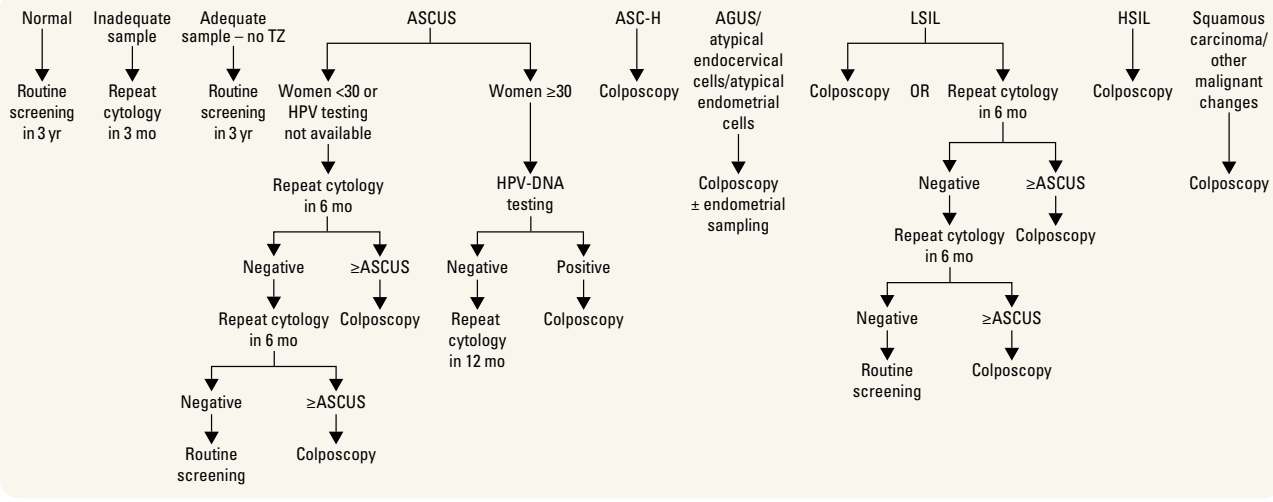



**Figure 2. Decision making chart for cervical cancer screening (not applicable to adolescents)**
AGUS = atypical glandular cells of unknown significance; ASCUS = abnormal squamous cells of unknown significance; ASC-H = abnormal squamous cells cannot rule out HSIL; HSIL = high grade squamous intraepithelial lesion; LSIL = low grade squamous intraepithelial lesion; TZ = transitional zone
Adapted from: Ontario Cervical Screening Cytology Guidelines, May 2012

# Prostate Cancer Screening Guidelines

### 2014 Canadian Task Force for Preventative Care Guidelines

- recommend NOT using prostate apecific antigen for prostate cancer screening in any age group (age <55: strong recommendation; low quality evidence, age 55-69: conditional recommendation; moderate quality evidence, age >70: strong recommendation; low quality evidence

# Health Promotion and Counselling

- health promotion is the most effective preventive strategy
- there are several effective ways to promote healthy behavioural change, such as discussions appropriate to a patient's present stage of change
- for more information, see www.motivationalinterviewing.org

## Motivational Strategies for Behavioural Change

**Table 2. Motivational Strategies for Behavioural Change**

| Patient's Stage of Change | Physician's Aim | Physician's Plan |
|---|---|---|
| **Pre-Contemplation** | Encourage patient to consider the possibility of change<br>Assess readiness for change<br>Increase patient's awareness of the problem and its risks | Raise issue in a sensitive manner<br>Offer (not impose) a neutral exchange of information to avoid resistance |
| **Contemplation** | Understand patient's ambivalence and encourage change<br>Build confidence and gain commitment to change | Offer opportunity to discuss pros and cons of change using reflective listening |
| **Preparation** | Explore options and choose course most appropriate to patient<br>Identify high-risk situations and develop strategies to prevent relapse<br>Continue to strengthen confidence and commitment | Offer realistic options for change and opportunity to discuss inevitable difficulties |
| **Action** | Help patients design rewards for success<br>Develop strategies to prevent relapse<br>Support and reinforce convictions towards long-term change | Offer positive reinforcement and explore ways of coping with obstacles<br>Encourage self-rewards to positively reinforce change |
| **Maintenance** | Help patient maintain motivation<br>Review identified high-risk situations and strategies for preventing relapse | Discuss progress and signs of impending relapse |
| **Relapse** | Help patient view relapse as a learning experience<br>Provide support appropriate to present level of readiness post-relapse | Offer a non-judgmental discussion about circumstances surrounding relapse and how to avoid relapse in the future<br>Reassess patient's readiness to change |

Adapted from: Hunt P. Motivating Change. *Nurs Stand* 2001;16:45-52, 54-55

## Nutrition

### General Population

- Canada's Food Guide is appropriate for individuals age ≥2
- counsel on variety, portion size, and plate layout
- vitamins and minerals: see "Functions and Food Sources of Some Common Vitamins" and "Functions and Food Sources of Some Common Minerals" - available from https://www.dietitians.ca/
- Guideline 1: Nutritious foods are the foundation for healthy eating, vegetables, fruits, whole grains, and proteins should be consumed regularly, consume plant based more often. Foods with mostly unsaturated fat should be replaced with those that contain mostly saturated fat. Water should be beverage of choice
- Guideline 2: Processed or prepared foods and beverages that contribute to excess sodium, free sugars, or saturated fat undermine healthy eating, should not be consumed regularly
- Guideline 3: Food skills are needed to navigate the complex food environment and support healthy eating. Cooking and food preparation using nutritious foods should be promoted. Food labels should be promoted as a tool to make informed choices

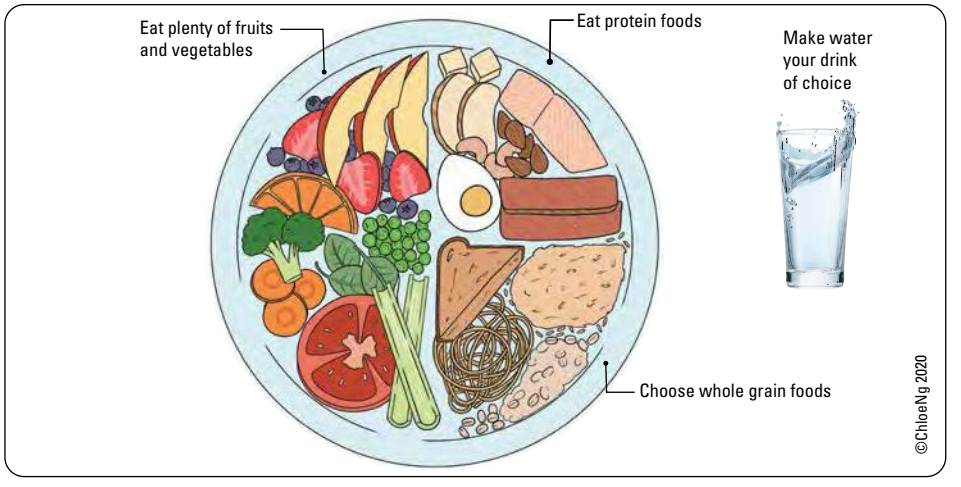



**Figure 3. Canada's Food Guide 2019 - plate layout**
Source: © All Rights Reserved. Canada's Food Guide. Health Canada, 2019. Adapted and reproduced with permission from the Minister of Health, 2019.

**Canadian Cancer Society (CCS) Recommendations for Vitamin D Use**
- Based on CCS research on Vitamin D and the prevention of colorectal, breast, and prostate cancer
- In consultation with their healthcare provider, the Society recommends that:
  - Adults living in Canada should consider taking Vitamin D supplementation of 1000 international units (IU) a day during the fall and winter
  - Adults at higher risk of having lower Vitamin D levels should consider taking Vitamin D supplementation of 1000 IU/d all year round. This includes people: who are older, with dark skin, who do not go outside often, and who wear clothing that covers most of their skin
  - Babies who are exclusively breast-fed: 400 IU/d

**Energy Content of Food**
- Carbohydrates 4 kcal/g
- Protein 4 kcal/g
- Fat 9 kcal/g
- Ethanol 7 kcal/g

**Calculating Total Daily Energy Expenditure (TDEE)**
- Roughly 35 kcal/kg/d
- Varies by age, weight, sex, and activity level
- Average 2000-2100 kcal/d for women, 2700-2900 kcal/d for men

**Handy Serving Size Comparisons**
- 3 oz meat, fish, poultry → palm of hand
- 1 cup dairy (milk/yogurt) → size of fist
- Bread/grains → one slice, palm of hand
- ½ cup rice/pasta → one hand cupped
- 1 cup of fruit/vegetables → two cupped hands
- 1 oz cheese → full length of thumb
- 1 tsp oil/butter → tip of thumb
- Nuts/chips/snacks → palm covered

## Cardiovascular Disease Prevention

### Table 3. Dietary Guidelines for Reducing Risk of Cardiovascular Disease

| | Recommendations | Effects |
|---|---|---|
| **Fat, Carbohydrates, Protein** | Overall fat intake: 26-27% of total energy<br>Saturated fat: 5-6% of total energy<br>Trans fat: reduce intake, replace with MUFA or PUFA<br>Carbohydrates: 55-59% of total energy<br>Protein: 15-18% of total energy | Lower LDL |
| **Omega-3 Fatty Acid Rich Foods** | ≥2 servings/wk of fish (especially oily fish like salmon) | Decreased sudden death, death from CAD<br>Lower TG |
| **Salt** | ≤2400 mg/d | Lower BP<br>Combining decreased sodium intake with the DASH diet (see below) achieves even greater BP-lowering effects |
| **Alcohol** | ≤3 drinks/d for men, max 15/wk<br>≤2 drinks/d for women, max 10/wk | Decreased risk of hypertriglyceridemia, HTN, osteoporosis, certain cancers |
| **Dietary Approaches** | DASH diet (Dietary Approaches to Stop Hypertension), recommended by the American Heart Association (AHA)<br><br>Diet: high in vegetables/fruits, low-fat dairy, whole grains, poultry, fish, and nuts;<br>Low in sweets, sugar-sweetened beverages, red meats<br>Macronutrients: low in saturated/total fat and cholesterol; high in potassium, magnesium, calcium, protein, and fibre<br><br>Mediterranean diet (fruits, vegetables, whole grains, legumes, nuts, olive oil, and herbs) | Lower BP, lower LDL |

MUFA = monounsaturated fatty acids; PUFA = polyunsaturated fatty acids
Eckel RH, et al. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2013
Dietary approaches to stop hypertension (DASH), available from: http://www.nhlbi.nih.gov/health/public/heart/hbp/dash/dash_brief.pdf
Lichtenstein AH, et al. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. Circulation 2006;114:82-96

**Osteoporosis Canada Recommendations for Calcium and Vitamin D Daily Requirements**
- Vitamin D: 800-1000 IU for individuals <50 yr, 800-2000 IU for individuals ≥50 yr
- Calcium: 1000 mg daily from all sources for individuals 19-50 yr and pregnant/lactating women; 1200 mg daily for individuals >50 yr (recommended to obtain calcium from nutrition whenever possible vs. supplementation)

# Obesity

## 2015 Canadian Task force on Preventive Health Care Recommendations

- body mass index (BMI) = weight (kg)/height (m)$^2$ = weight (lbs)/height (in)$^2$ x 703; poor predictor of obesity
- waist circumference (WC) = flexible tape placed on horizontal plane at iliac crest; normal depends on ethnic background
- increased WC for BMI 25-35 increases the risk of cardiovascular disease and type 2 diabetes

**Effectiveness of Behavioural and Pharmacologic Treatment for Overweight and Obesity in Adults**
CMAJ Open 2014;2:E306-17
**Purpose**: To evaluate the effectiveness of behavioural and pharmacological treatments for overweight and obese adults.
**Methods**: Review of RCTs of primary-care-relevant behavioural (diet, exercise, lifestyle) and pharmacological (orlistat, metformin) treatments with or without behavioural interventions in overweight or obese adults with 12 mo follow-up from baseline for weight outcomes or harms. Secondary health outcomes (total cholesterol, LDL, fasting blood glucose, incidence of type 2 DM, systolic and diastolic BP) were also studied.
**Results**: 68 RCTs were included, and showed that intervention participants had greater weight loss (-3.02 kg, 95% CI -3.52 to -2.52), waist circumference reduction (-2.78, -3.34 to -2.22) and body mass index reduction (-1.11, -1.39 to -0.84). Relative risk for weight loss of 5% or greater body weight was 1.77 (1.58 to 1.99, NNT 5, 95% CI 4-7). Incidence of type 2 DM was lower among pre-diabetic intervention participants.
**Conclusion**: Behavioural and pharmacological treatments for overweight and obese adults may lead to clinically important reductions in weight and type 2 DM incidence in pre-diabetics.

### Table 4. Classification of Weight by BMI, Waist Circumference, and Associated Disease Risks in Adults

| | | | Disease Risk* Relative to Normal Weight and Waist Circumference | |
|---|---|---|---|---|
| | **BMI (kg/m$^2$)** | **Obesity Class** | **Men ≤102 cm (40 in) Women ≤88 cm (35 in)** | **Men >102 cm (40 in) Women >88 cm (35 in)** |
| **Underweight** | <18.5 | | | |
| **Normal** | 18.5-24.9 | | | |
| **Overweight** | 25.0-29.9 | | Increased | High |
| **Obesity Class I** | 30.0-34.9 | I | High | Very High |
| **Obesity Class II** | 35.0-39.9 | II | Very High | Very High |
| **Obesity Class III** (Extreme Obesity) | 40.0 + | III | Extremely High | Extremely High |

* Disease risk for type 2 diabetes, hypertension, and CVD
From: Classification of Overweight and Obesity by BMI, Waist Circumference, and Associated Disease Risks, National Institute of Health, National Heart Lung and Blood Institute, Obesity Education Initiative, http://www.nhlbi.nih.gov/health/public/heart/obesity/lose_wt/bmi_dis.htm

**Adverse Medical Consequences of Obesity**
- Type 2 DM
- CAD
- Stroke
- HTN
- Gallbladder disease
- Non-alcoholic steatohepatitis
- Pregnancy complications
- Dyslipidemia
- Osteoarthritis
- Sleep apnea
- Certain cancers
  - CHF
- Low back pain
- Increased total mortality

## Epidemiology

- 20.2% of Canadians aged 18 and older (excluding pregnant women) were obese in 2014 (StatsCan, 2014)
- obesity remains higher in Aboriginal populations compared with non-Aboriginal populations with 25.7% of Aboriginal adults (excluding First Nations on-reserve) estimated to be obese (CCHS 2007/2008)
- close to a third of 5-17yr were identified as overweight or obese (2009 to 2011 CHMS)
- overweight and obesity rates in children are directly proportional to screen time (see *Exercise*, FM10)

**Low BMI Associations**
- Osteoporosis
- Eating disorders
- Under-nutrition
- Pregnancy complications

## Screening Recommendations

- CANRISK or FINRISC scores can be used to assess the risk for type 2 DM in overweight and obese patients
- recommends measuring height and weight and then calculating BMI at appropriate primary care visits

## Management

### Behavioural/ Lifestyle

- weight loss of >5% is clinically significant for reducing many cardiovascular risk factors (e.g. elevated blood pressure, glucose, and lipids)
- efficacious behavioural interventions: >12 mo duration, include diet, exercise, lifestyle components, and group and individual sessions
- structured behavioural and lifestyle interventions should be offered or arranged for overweight individuals BMI >25
- strong recommendation for those with increased risk of Type 2 DM
- BMI >35 and risk factors or BMI >40 are candidates for bariatric surgery failing behavioural modification

## Pharmacologic

- recommends against pharmacologic intervention to manage patients who are overweight and obese, although some patients may prefer medications and be good candidates for pharmacologic treatment
- high benefit of behavioural modification alone, NNH (number needed to harm) 10 (mostly GI side effects) for pharmacotherapy

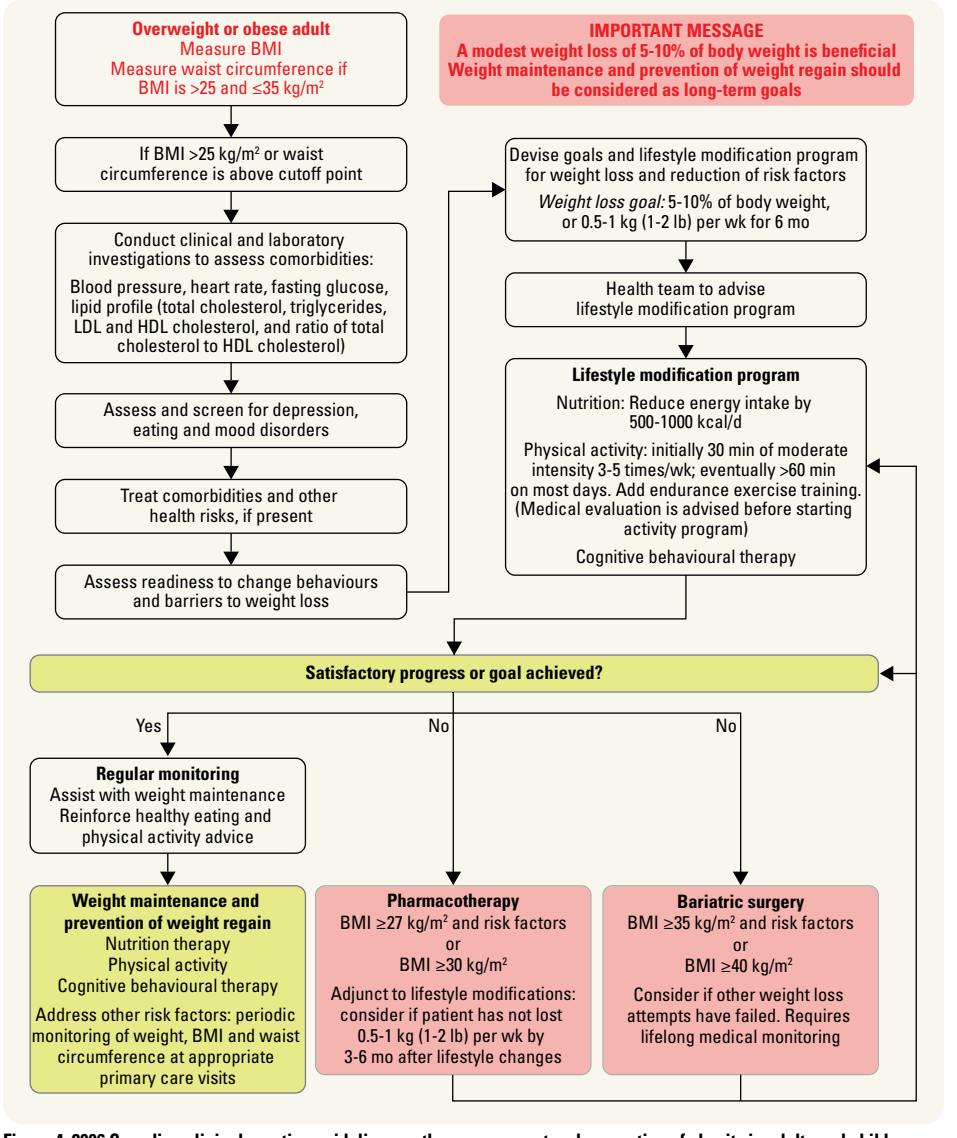



**Figure 4. 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children**
Adapted from: CMAJ 2007;176:S1-S13

**Pharmacotherapy for Obesity**

- Orlistat: gastrointestinal lipase inhibitor, reduces fat absorption by 30% by inhibition of pancreatic lipase
- Orlistat is associated with several adverse effects and not approved for clinical use longer than 2 yr
- Orlistat should be avoided in people with inflammatory or chronic bowel disease

**Effects of Popular Diets without Specific Calorie Targets on Weight Loss Outcomes: Systematic Review of Findings from Clinical Trials - 2017**

**Purpose**: To assess the short term (≤6 mo) and long term (≥6 mo) weight loss outcomes for current popular diets.

**Methods**: A systematic review was conducted. All diets in the 2016 U.S. News & World Report Rankings were examined. From the potential 38 diets, eligible studies included trials with a sample size greater than 15, interventional clinical trials, intervention periods longer than 12 wk, BMI ≥25 mg/m², participants age ≥18 and objective measures of pre- and post-intervention.

**Results**: Sixteen articles were included in the review which included the Atkin, DASH, Glycemic-Index, Mediterranean, Ornish, Paleolithic, and Zone diets. The Atkins diet showed the most significant reduction in weight loss both in the short-term and long-term.

**Conclusion**: Other diets had limited evidence in producing clinically significant short-term and long-term weight loss. Future studies are needed to evaluate the efficacy of each diet.

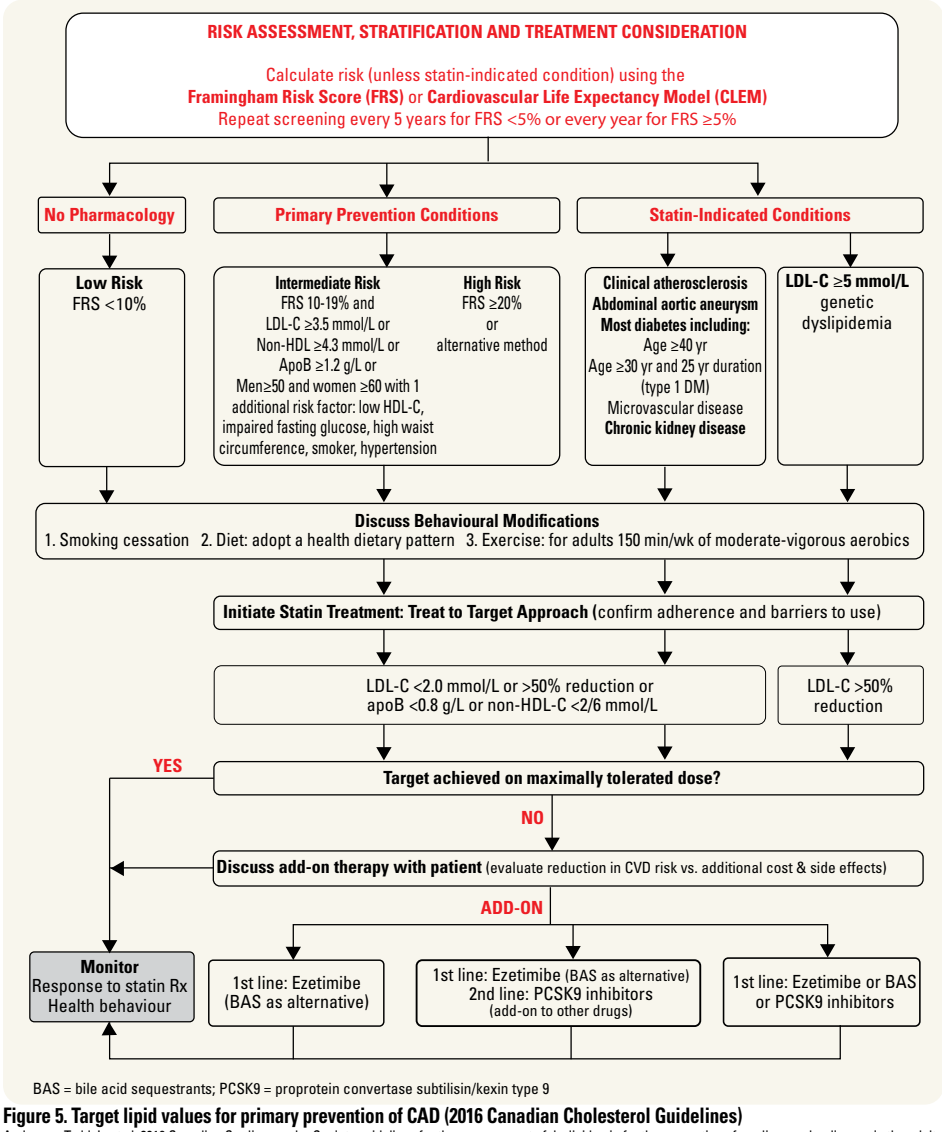
**Hyperlipidemia Signs**

- Atheromata: plaques in blood vessel walls
- Xanthelasmata: a sharply demarcated yellowish deposit of cholesterol underneath the skin, usually on or around the eyelid
- Tendinous xanthoma: lipid deposit in tendon (especially Achilles)
- Eruptive xanthoma: hypertriglyceridemia induced reddish yellow, pruritic, and painful papular or nodular rash
- Lipemia retinalis: thin atheromata seen in the retinal blood vessels
- Corneal arcus (arcus senilis): lipid deposit in cornea

# Dyslipidemia

- see Endocrinology, E3
- **definition**: abnormal elevation of plasma cholesterol or triglyceride levels

## Assessment




BAS = bile acid sequestrants; PCSK9 = proprotein convertase subtilisin/kexin type 9

**Figure 5. Target lipid values for primary prevention of CAD (2016 Canadian Cholesterol Guidelines)**
Anderson, Todd J., et al. 2016 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. Canadian Journal of Cardiology 32.11 (2016): 1263-1282

- measure fasting serum TC, LDL-C, HDL-C, and TG
- screen with full fasting lipid profile q1-3yr in males and females >40 yr or who are menopausal, or at any age for adults with additional dyslipidemia risk factors (see sidebar)
- screen for secondary causes: hypothyroidism, chronic kidney disease, DM, nephrotic syndrome, liver disease
- risk category
  - estimate using the Framingham Risk Score (FRS) for assessing 10 yr risk of developing CAD
    - FRS is calculated based on gender, age, HDL-C, total cholesterol, sBP, smoking, DM
    - family history of CVD <55 male relative or <65 in female relative doubles FRS
    - to be completed for men and women age 40-75 q3-5yr
    - cardiovascular age calculated as patient's age ± the difference between his or her estimated remaining life expectancy
- used to increase adherence to therapy and reaffirm positive effect of following therapy
  - treatment decisions focus on LDL-C level and/or FRS risk; the alternate primary targets are apolipoprotein B (apo B) and non-HDL-C
  - if moderate risk and LDL-C <3.5, treatment decision thresholds shifted to apo B >1.2 g/L or non-HDL-C >4.3 mmol/L
  - other targets include: TC:HDL-C ratio, apo B:apo AI ratio, hs-CRP (used more for risk stratification of CAD), non-HDL-C, and serum TG levels

To calculate Framingham Risk Score, go to https://www.framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/

**Risk Factors for Screening for Dyslipidemia**
- First Nations or South Asian ancestry
- Current cigarette smoking
- Diabetes
- Arterial Hypertension
- Family history of premature CVD
- Family history of hyperlipidemia
- Erectile dysfunction
- Chronic kidney disease
- Inflammatory disease (lupus, rheumatoid arthritis, psoriatic arthritis, IBD)
- HIV infection
- Chronic obstructive pulmonary disease
- Clinical evidence of atherosclerosis or abdominal aneurysm
- Clinical manifestation of hyperlipidemia
- Obesity (BMI>27)

**Non-fasting Lipids vs. Fasting Lipids**
Non-fasting (TC and non-HDL cholesterol) can be used for Framingham Risk Assessment and hold same prognostic value as fasting lipids
In fasted vs. non-fasted samples, non-HDL and TC varies by 2%, LDL-C by 10% and TG by 20%
Recently, non-fasting LDL-C has the same prognostic value as fasting LDL-C
Ontario Association of Medical Laboratories Guidelines for Lipid Testing in Adults (2013): https://oaml.com/wp-content/uploads/2016/05/OAMLGuidelineforAdultLipidTestingFinal2013.pdf

LDL cannot be calculated when TG ≥4.5 mmol/L

**Safety of Statins: An Update**
Therapeutic Advances in Drug Safety 2012;3:133-144
Trials have shown that statin therapy slightly increases the incidence of diabetes; however, the absolute risk is small. Relative to the reduction in coronary events, the clinical significance is not great enough to recommend against their use.

Use with caution when prescribing combined statin and fibrate therapy as there has been concern regarding the safety of certain combinations (potential increased risk of myopathy and rhabdomyolysis)

### Management

- intensity and type of treatment is guided by "risk category" assigned (see Figure 5)

1. Health behaviours (can decrease LDL-C by up to 10%)
   - smoking cessation: probably the most important for preventing CAD
   - dietary modification: reduce saturated fat, red meat, refined sugar, alcohol; consume nuts, fruits/vegetables, poultry, fish
   - physical activity: at least 150 min of moderate to vigorous intensity aerobic exercise per wk, in bouts of 10 min or more to reduce CVD risk (see Table 5)
   - employ consistent lifestyle modifications for at least 3 mo before considering drug therapy; high risk patients should start treatment immediately with concurrent health behaviour interventions
2. Pharmacologic therapy (can decrease LDL-C by up to 40%)
   - for a comparison of dyslipidemia medications, see Endocrinology, E3
   - 1st line monotherapy: statins (HMG-CoA reductase inhibitors)
     - risks: myopathy and hepatotoxicity
     - if severe side effects: ezetimibe (cholesterol absorption inhibitor) can be used for 19% reduction in LDL-C
     - post-acute coronary syndrome, cholesterol absorption inhibitors (e.g. ezetimibe) in addition to simvastatin reduced mortality, attained lipid targets <1.8, and improved outcomes in high risk individuals

- lower evidence for other agents: bile acid sequestrants, nicotinic acid, fibrates, psyllium
  - monitoring
- ALT, CK, creatinine at baseline then 6 wk later for signs of transaminitis or myositis; tolerate rise in CK up to 10 times upper limit of normal vs. 2-3 times if symptomatic, or serum creatinine rise of ≤25%
- no routine repeated measures of ALT and CK necessary in asymptomatic patients using statin therapy
- if adequate response is achieved, evaluate fasting lipids q6-12mo

**Clinical Definition of Metabolic Syndrome**

- Central obesity
  Men – waist circumference ≥94 cm
  Women – waist circumference ≥80 cm
- Plus any TWO of the following four factors

| Risk Factor | Defining Level |
|---|---|
| TG level | ≥1.7 mmol/L (150 mg/dL) |
| HDL-C level: | |
| Men | <1.0 mmol/L (40 mg/dL) |
| Women | <1.3 mmol/L (50 mg/dL) |
| Blood pressure | ≥130/85 mmHg |
| Fasting glucose level | ≥5.6 mmol/L (100 mg/dL) |

### Isolated Hypertriglyceridemia

- does not increase cardiovascular risk
- normal HDL-C and TC, elevated TG
- mild ≥2.2 mmol/L (≥200 mg/dL); marked ≥5.6 mmol/L (≥500 mg/dL)
- principal therapy is lifestyle modification
  - weight loss, exercise, avoidance of smoking and alcohol, effective blood glucose control in diabetics, increased omega-3 fatty acid intake
  - severe hypertriglyceridemia (typically >10 mmol/L) is associated with an increased risk of acute pancreatitis
- drug therapy (lowers risk for pancreatitis, not CAD)
  - nicotinic acid
  - fibrates

## Exercise

**Table 5. Canadian 24-Hour Movement Guidelines (2017 CSEP Guidelines)**

| Age Category | Physical Activity Guidelines | Example Activities | Sleep/Sit Guidelines |
|---|---|---|---|
| **Infant (<1)** | Active several times daily<br>Tummy time for at least 30 min/d | Interactive floor-based play including tummy time, reaching for toys, crawling | **Sleep**: 14-17 h/d of good quality sleep including naps<br>**Sit**: not restrained (i.e. in a stroller) for more than 1 h, screen time not recommended, engaging in reading/storytelling while sedentary |
| **Toddler (1-2)** | Accumulate 180 min of physical activity at any intensity spread throughout the day including energetic play | Moving around the home<br>Climbing stairs<br>Exploring environment<br>Brisk walking, running, dancing | **Sleep**: 11-14 h/d of good quality sleep including naps<br>**Sit**: not restrained (i.e. in a stroller) for more than 1 h, screen time not recommended, engaging in reading/storytelling while sedentary |
| **Preschool (2-4)** | Accumulate >180 min in a variety of activities at any intensity, including at least 60 min of energetic play throughout the day | Moving around the home<br>Climbing stairs<br>Exploring environment<br>Brisk walking, running, dancing | **Sleep**: 10-13 h/d of good quality sleep which may include a nap<br>**Sit**: not restrained (i.e. in a stroller) for more than 1 h, screen time no more than 1 h (less is better), reading/storytelling while sedentary |
| **Children (5-11) and Youth (12-17)** | Moderate to vigorous aerobic and muscle/bone strengthening exercises 60 min/d 3x/wk<br>Light physical activity for several hours per day | Moderate: bike riding, playground<br>Vigorous: running, swimming | **Sleep**: 9-11 h/d (5-13 yr), 8-10 h/d (16-17 yr)<br>**Sit**: no more than 2 h/d of recreational screen time, limit sitting for extended periods |
| **Adults (18-64)** | Accumulate 150 min of moderate to vigorous intensity aerobic physical activity per wk, in bouts of 10 min or more<br>It is beneficial to add muscle and bone strengthening activities using major muscle groups, at least 2 d/wk | Moderate: brisk walking, bike riding<br>Vigorous: jogging, cross country skiing | No specific guidelines |
| **Older Adults (≥65)** | Same as Adults above | Same as Adults above<br>Those with poor mobility should perform physical activities to enhance balance and prevent falls | No specific guidelines |

**Statin-Related Adverse Events: A Meta-Analysis**
Clin Ther 2006;28:26-35
**Purpose**: To synthesize adverse event (AE) data with statin use based on RCT data.
**Methods**: Meta-analysis of RCTs focused on adverse effects of statins. Eligible patients were those taking statin monotherapy for primary or secondary prevention of CVD, compared to placebo. AEs including elevated liver enzymes or myopathy (myalgias, elevated CK, rhabdomyolysis) were the main outcomes.
**Results**: Statin therapy increased the risk of any AE by 39% (OR 1.4; 95% CI 1.09-1.80; p=0.008) compared with placebo. Treating 1000 patients with a statin would cause 5 AE. Serious events (CK >10 times the upper limit of normal or rhabdomyolysis) are infrequent (NNH 3400) and rhabdomyolysis, although serious, is rare (NNH 7428).
**Conclusion**: Statin therapy was associated with greater odds of AEs compared with placebo but with substantial clinical benefit. Similar rates of serious AEs were observed between statin and placebo.

### Epidemiology
- 25% of the population exercises regularly, 50% occasionally, 25% are sedentary

### Management
- assess current level of fitness, motivation, and access to exercise
- encourage warm up and cool down periods to allow transition between rest and activity and to avoid injuries
- exercise with caution for patients with CAD, DM (risk of hypoglycemia), exercise-induced asthma
- patients with known CAD should have cardiac assessment prior to commencing exercise
- benefits of exercise
  - reduces risk of premature death, heart disease, stroke, HTN, certain types of cancer, type 2 DM, osteoporosis, and overweight/obesity
  - leads to improved fitness, strength, and mental health (morale and self-esteem)

## Smoking Cessation

### Epidemiology
- smoking is the single most preventable cause of premature illness and death
- 70% of smokers see a physician each year
- 2012 Canadian Tobacco Use Monitoring Survey (CTUMS) on population age ≥15
  - 16% are current smokers (lowest since 1965)
  - highest prevalence in age group 20-24 (20%)
  - 11% of youth age 15-19 smoke (decreased from 25% in 2000): more males smoke than females; number of cigarettes consumed per day also decreasing

### Management
- general approach
  - identify tobacco users; elicit smoking habits, previous quit attempts, and results
  - 2012 CAN-ADAPTT Guidelines
    - tobacco use status should be updated for all patients regularly
    - health care providers should clearly advise patients to quit
    - health care providers should also monitor the patient's mental health status/other addictions while quitting smoking
- medication dosage should be monitored and adjusted as necessary
  - every smoker should be offered treatment
- combining counselling and smoking cessation medication is more effective than either alone
  - educate patient to watch for withdrawal symptoms
- low mood, insomnia, irritability, anxiety, difficulty concentrating, restlessness, decreased heart rate, increased appetite
  - ≥4 counselling sessions >10 min each with 6-12 mo follow-up yields better results
  - 14% abstinent with counselling vs. 10% without counselling
  - approach depends on patient's stage of change (see *Motivational Strategies for Behavioural Change*, FM6)
- willing to quit
  - provision of social support, community resources (self-help, group, helpline, web-based strategies)
  - pregnant patients: counselling is recommended as first line treatment
    - nicotine replacement therapy (NRT) should be made available to pregnant women who are unable to quit using non-pharmacologic methods
    - intermittent NRT use (lozenges, gum) is preferred over continuous dosing of the patch
    - no strong evidence that either major positive or negative outcomes were associated with gestational use of bupropion or varenicline; consider using only if benefits outweigh risks and consult Motherisk Helpline
- pharmacologic therapy
  1. Nicotine Replacement Therapy
     - 19.7% abstinent at 12 mo with NRT vs. 11.5% for placebo
     - no difference in achieving abstinence for different forms of NRT
     - reduces cravings and withdrawal symptoms without other harmful substances that are contained in cigarettes
     - use with caution: immediately post-MI, worsening angina, arrhythmia
     - advise no smoking while using NRT
  2. Antidepressants (mechanism of action appears to be independent of antidepressant effect)
     - bupropion SR (Zyban®)
     - 21% abstinent at 12 mo vs. 8% for placebo
     - similar effectiveness of NRT vs. bupropion
  3. Varenicline (Champix®)
     - partial nicotinic receptor agonist (to reduce cravings) and partial competitive nicotinic receptor antagonist (to reduce the response to smoked nicotine)
     - more effective than bupropion (23% abstinent from 9-52 wk with varenicline vs. 16% with bupropion vs. 9% with placebo)
     - significant side effects may lower patient compliance



**Antidepressants for Smoking Cessation**
Cochrane Database Syst Rev 2014;1:CD000031
**Purpose**: To assess the efficacy and safety of antidepressants for long-term smoking cessation.
**Methods**: Meta-analysis of RCTs comparing antidepressant medications to placebo or alternative medications for smoking cessation. Studies comparing different doses, use of pharmacotherapy for relapse prevention or re-initiation of smoking cessation, or those targeting reduction in cigarette consumption by smokers, were also considered eligible. Eligible studies were required to have a minimum of 6 mo follow-up.
**Results**: 90 trials were included. Antidepressants found to significantly increase long-term cessation included bupropion alone (risk ratio (RR) 1.62, 95% CI 1.49-1.76) and nortriptyline alone (RR 2.03, 1.48-2.78), which appeared equally effective to each other and to nicotine replacement therapy (NRT). No significant additional long-term benefit was found with adding bupropion (RR 1.19, 0.94-1.51) or nortriptyline (RR 1.21, 0.94-1.55) to NRT. Significantly lower quit rates (RR 0.68, 0.56-0.83) and increased adverse events close to statistical significance (1.30, 1.00-1.69) were found with buproprion compared to varenicline. No evidence showed significant effectiveness for selective serotonin reuptake inhibitors alone (RR 0.93, 0.71-1.22) or in addition to NRT (RR 0.70-0.64-1.82), or with monoamine oxidase inhibitors alone (RR 1.29, 0.93-1.79), venlafaxine (RR 1.22, 0.64-2.32), St. John's wort/hypericum (RR 0.81, 0.26-2.53) or SAMe dietary supplement (RR 0.70, 0.24-2.07).
**Conclusion**: The antidepressants bupropion and nortriptyline can aid smoking cessation and have a similar efficacy to NRT. Bupropion is less effective than varenicline. Neither SSRIs (e.g. fluoxetine) nor MAOIs aid smoking cessation.



**The 5 A's for Patients Willing to Quit**
**A**sk if the patient smokes
**A**dvise patients to quit
**A**ssess willingness to quit
**A**ssist in quit attempt
**A**rrange follow-up



**The 2-3 Pattern of Smoking Cessation**
- Onset of withdrawal is 2-3 h after last cigarette
- Peak withdrawal is at 2-3 d
- Expect improvement of withdrawal symptoms at 2-3 wk
- Resolution of withdrawal at 2-3 mo
- Highest relapse rate within 2-3 mo



**Assist Patient in Developing Quit Plan**

**STAR**
**S**et quit date
**T**ell family and friends (for support)
**A**nticipate challenges (e.g. withdrawal)
**R**emove tobacco-related products (e.g. ashtrays/lighters)



**Physician Advice for Smoking Cessation**
Cochrane Database Syst Rev 2013;5:CD000165
**Purpose**: To assess the effectiveness of physician advice in promoting smoking cessation, compare minimal physician interventions with more intensive interventions, assess the effectiveness of various aids in smoking cessation, and determine the effect of anti-smoking advice on mortality.
**Methods**: Systematic review of RCTs of smoking cessation advice from a health care provider. Abstinence was assessed at least 6 mo after advice was provided.
**Results**: 42 trials with over 31,000 smokers were identified. Most common setting for advice delivery was primary care. A significant increase in quitting rates was noted with advice versus no advice (relative risk (RR) 1.66, 95% CI 1.42-1.94), which was further increased where the intervention was considered more intensive (RR 1.84, 1.60-2.13; n.s.). Intensive advice showed a small advantage to minimal advice when directly compared (RR 1.37, 1.20-1.56). A small benefit with follow-up visits was also found. No statistically significant difference in mortality at 20 yr follow-up was noted.
**Conclusion**: Simple advice can increase cessation rates by 1-3%. More intensive advice and providing follow-up support may further increase quit rates.

**Table 6. Types of Nicotine Replacement Therapy**

| Type | Dosage | Comment | Side Effects |
|---|---|---|---|
| **Nicotine Gum (OTC)** | 2 mg if <25 cig/d<br>4 mg if >25 cig/d<br>1 piece q1-2h for 1-3 mo<br>(max 24 pieces/d) | Chew until "peppery" taste then "park" between gum and cheek to facilitate absorption<br>Continue to chew-park intermittently for 30 min | Mouth soreness<br>Hiccups<br>Dyspepsia<br>Jaw ache<br>Most are transient |
| **Nicotine Patch (OTC)** | Use for 8 wk<br>21 mg/d x 4 wk<br>14 mg/d x 2 wk<br>7 mg/d x 2 wk | Start with lower dose if <10 cig/d<br>Change patch q24h and alternate sides | Skin irritation<br>Insomnia<br>Palpitations<br>Anxiety |
| **Nicotine Inhaler (OTC)** | 6-16 cartridges/d<br>up to 12 wk | Nicotine inhaled through mouth, absorbed in mouth and throat not in lungs | Local irritation<br>Coughing |
| **Nicotine Nasal Spray (Rx)** | | Newer form of NRT | Local irritation<br>Coughing |

**Table 7. Pharmacologic Treatments for Smoking Cessation**

| Drug | Mechanism | Dosage | Prescribing* | Contraindications |
|---|---|---|---|---|
| **Bupropion** | Inhibits re-uptake of dopamine and/or norepinephrine<br>Side effects: insomnia, dry mouth | 1. 150 mg qAM x 3 d<br>2. Then 150 mg bid x 7-12 wk<br>3. For maintenance consider 150 mg bid for up to 6 mo | 1. Decide on a quit date<br>2. Continue to smoke for first 1-2 wk of treatment and then completely stop (therapeutic levels reached in 1 wk) | Seizure disorder<br>Eating disorder<br>MAOI use in past 14 d<br>Simultaneous use of bupropion (Wellbutrin®) for depression |
| **Varenicline** | Partial nicotinic receptor agonist, and partial nicotinic receptor competitive antagonist<br>Side effects: nausea, vomiting, constipation, headache, dream disorder, insomnia, increased risk of psychosis, depression, suicidal ideation | 1. 0.5 mg qAM x 3 d<br>2. Then 0.5 mg bid x 4 d<br>3. Continue 1 mg bid x 12 wk ± additional 12 wk as maintenance | 1. Decide on a quit date<br>2. Continue to smoke for first wk of treatment and then completely stop | Caution with pre-existing psychiatric condition |

*Bupropion and verenicline may be used in combination with nicotine replacement therapy

**Nicotine Replacement Therapy for Smoking Cessation**
Cochrane Database Syst Rev 2012;11:CD000146
**Purpose**: To determine the effect of nicotine replacement therapy (NRT) versus placebo and other pharmacotherapies for smoking cessation, and to determine whether abstinence rates are influenced by NRT form, single-therapy or combination therapy, dosage, timing of use, additional advice and support offered, or clinical setting of recruitment and treatment.
**Results**: 150 trials were identified. All forms of NRT relative to placebo was associated with a significant increase in abstinence (risk ratio (RR) 1.60, 95% CI 1.53-1.68). A similar increase was seen by NRT form for the nicotine gum (RR 1.49, 1.40-1.60), nicotine patch (RR 1.64, 1.52-1.78), oral tablets/lozenges (RR 1.95, 1.61-2.36), nicotine inhaler (RR 1.90, 1.36-2.67) and nicotine nasal spray (RR 2.02, 1.49-2.73). Effects were independent of duration of therapy, intensity of additional support or setting in which NRT was offered. Some evidence suggested combining a nicotine patch with rapid NRT delivery was more effective than a single type of NRT (RR 1.34, 1.18-1.51), though not statistically significant. No evidence of a significant difference in efficacy relative to buproprion was found (RR 1.01, 0.87-1.18), and combination therapy with the two was more effective than buproprion alone (RR 1.24, 1.06-1.45). While side-effects were noted, no evidence suggested increased risk of heart attacks with NRT.
**Conclusions**: All commercially available forms of NRT (gum, transdermal patch, nasal spray, inhaler, and sublingual tablets/lozenges) are effective as part of a strategy to promote smoking cessation. They increase the rate of quitting by 50-70% regardless of setting and independent on the level of additional support provided to the smoker. Compared to a single form of NRT, combining a nicotine patch with a rapid delivery form of NRT may be more effective.

- unwilling to quit
  - motivational intervention (5 Rs)
    1. **R**elevance to patient
       - relevant to patient's disease status or risk, family or social situation (e.g. having children in the home), health concerns, age, gender
    2. **R**isks of smoking
       - short-term: SOB, asthma exacerbation, impotence, infertility, pregnancy complications, heartburn, URTI
       - long-term: MI, stroke, COPD, lung CA, other cancers
       - environmental: higher risk in spouse/children for lung CA, SIDS, asthma, respiratory infections
    3. **R**ewards: benefits
       - improved health, save money, food tastes better, good example to children
    4. **R**oadblocks: obstacles
       - fear of withdrawal, weight gain, failure, lack of support
    5. **R**epetition
       - reassure unsuccessful patients that most people try many times before successfully quitting (average number of attempts before success is 7)
- recent quitter
  - highest relapse rate within 3 mo of quitting
    - minimal practice: congratulate on success, encourage ongoing abstinence, review benefits and problems
    - prescriptive interventions: address problem of weight gain, negative mood, withdrawal, lack of support

# Alcohol Use

- see Psychiatry, PS26

## Definition

- alcohol use disorder diagnostic categories occur along a continuum

## Epidemiology

- 10-15% of patients in family practice are problem drinkers
- 20-50% of hospital admissions, 10% of premature deaths, 30% of suicides, and 50% of fatal traffic accidents in Canada are alcohol-related
- more likely to miss diagnosis in women, elderly, and patients with high socioeconomic status

**Standard Drink Equivalents**
One standard drink = 14 g of pure alcohol
- Beer (5% alcohol) = 12 oz
- Wine (12-17% alcohol) = 5 oz
- Fortified wine = 3 oz
- Hard liquor (40%) = 1.5 oz

### Assessment
- screen for alcohol dependence with CAGE questionnaire
  - if CAGE positive, explore with further questions for alcohol abuse/dependence
- assess drinking profile
  - setting, time, place, occasion, with whom
  - impact on: family, work, social
  - quantity-frequency history
    - how many drinks per day?
    - how many days per week?
    - maximum number of drinks on any one day in the past month?
- if identified positive for alcohol problem
  - screen for other drug use
  - identify medical/psychiatric complications
  - ask about drinking and driving
  - ask about past recovery attempts and current readiness for change

**CAGE Questionnaire**
Have you ever felt you needed to **C**ut down on your drinking?
Have people **A**nnoyed you by criticizing your drinking?
Have you ever felt **G**uilty about drinking?
Have you ever felt you needed a drink first thing in the morning (**E**ye-opener) to steady your nerves or to get rid of a hangover?
Two "yes" responses is considered positive

### Investigations
- GGT and MCV for baseline and follow-up monitoring
- AST, ALT (usually AST:ALT approaches 2:1 in an alcoholic)
- CBC (anemia, thrombocytopenia), INR (decreased clotting factor production by liver)

### Management
- intervention should be consistent with patient's motivation for change
- individualized counselling and regular follow-up is crucial
- 10% of patients in alcohol withdrawal will have seizures or delirium tremens
- Alcoholics Anonymous/12-step program
  - outpatient/day programs for those with chronic, resistant problems
  - family treatment (Al-Anon, Alateen, screen for spouse/child abuse)
- in-patient program if:
  - dangerous or highly unstable home environment
  - severe medical/psychiatric problem
  - addiction to drug that may require in-patient detoxification
  - refractory to other treatment programs
- pharmacologic
  - diazepam for withdrawal
  - disulfiram (Antabuse®): impairs metabolism of alcohol by blocking conversion of acetaldehyde to acetic acid, leading to flushing, headache, N/V, hypotension if alcohol is ingested (available in U.S., but no longer available in Canada)
  - naltrexone: competitive opioid antagonist that reduces cravings and pleasurable effects of drinking
- may trigger withdrawal in opioid-dependent patients
  - acamprosate: glutamate receptor modulator that also reduces craving
- see Psychiatry, PS26




**Figure 6. Continuum of alcohol use**

### Prognosis
- relapse is common and should not be viewed as failure
- monitor regularly for signs of relapse
- 25-30% of abusers exhibit spontaneous improvement over 1 yr
- 60-70% of individuals with jobs and families have an improved quality of life 1 yr post-treatment

**Some Adverse Medical Consequences of Problem Drinking**
- GI: gastritis, dyspepsia, pancreatitis, liver disease, bleeds, diarrhea, oral/esophageal cancer
- Cardiac: HTN, alcoholic cardiomyopathy
- Neurologic: Wernicke-Korsakoff syndrome, peripheral neuropathy
- Hematologic: anemia, coagulopathies
- Other: trauma, insomnia, family violence, anxiety/depression, social/family dysfunction, sexual dysfunction, fetal damage

# Common Presenting Problems

## Abdominal Pain

- see Gastroenterology, G4, General Surgery, GS4, and Emergency Medicine, ER59

### Epidemiology
- 20% of individuals have experienced abdominal pain within the last 6-12 mo
- 90% resolve in 2-3 wk
- only 10% are referred to specialists, of those <10% admitted to hospital

### Etiology
- most common diagnosis in family medicine at 28% is "nonspecific abdominal pain," which has no identifiable cause and is usually self-limited
- GI disorders (e.g. PUD, pancreatitis, IBD, appendicitis, gastroenteritis, IBS, diverticular disease, biliary tract disease)
- urinary tract disorders (e.g. UTI, renal calculi)
- gynecological disorders (e.g. PID, ectopic pregnancy, endometriosis)
- cardiovascular disorders (e.g. CAD, AAA, ischemic bowel)
- other: DKA, porphyria, hypercalcemia, medications (e.g. NSAIDs), alcohol, toxic ingestion, foreign body, psychogenic

If pain precedes nausea/vomiting, cause of abdominal pain is more likely to be surgical

### Pathophysiology
- type of pain
  - somatic pain: sharp, localized pain
  - visceral pain: dull, generalized pain
- location of pain
  - epigastric (foregut): distal esophagus, stomach, proximal duodenum, biliary tree, pancreas, liver
    - RUQ: biliary, hepatic, colonic, pulmonary, renal
    - LUQ: cardiac, gastric, pancreatic, renal, vascular
  - periumbilical (midgut): distal duodenum to proximal 2/3 of transverse colon
  - hypogastric (hindgut): distal 1/3 of transverse colon to rectosigmoid region
    - RLQ: colonic, appendix, gynecologic, renal
    - LLQ: colonic, gynecologic, renal
  - any location: aneurysm, dissection, ischemia, zoster, muscle strain, hernia, bowel obstruction, peritonitis, porphyria, DKA

**Abdominal Pain Red Flags**
- Severe pain
- Signs of shock
- Peritoneal signs
- Abdominal distention
- Pain out of proportion to clinical findings
- New onset pain, change in pain, or altered bowel habits in elderly
- Weight loss
- Blood per rectum/melena
- Anemia
- Supraclavicular nodes
- Family history of serious bowel disease

### Investigations
- guided by findings on history and physical
- possible blood work: CBC, electrolytes, BUN, Cr, amylase, lipase, AST, ALT, ALP, bilirubin, glucose, INR/PTT, toxicology screen, β-hCG
- imaging
  - CXR (for free air under the diaphragm) in setting of perforation in surgical abdomen
  - abdominal x-ray, KUB (consider: gas pattern, free air, kidney stones, constipation)
  - ultrasound (renal stones, gallbladder disease, gynecological problems, liver disease, pancreatitis, diverticular disease, appendicitis)
  - CT scan (AAA, appendicitis), non-contrast helical CT-Scan (first choice for renal stones)
- other tests
  - urinalysis
  - endoscopy (for peptic ulcers, gastritis, tumours, etc.)
  - *H. pylori* testing (urea breath test, serology, biopsy)

In patients >50, keep a high index of suspicion for AAA – its presentation may mimic renal colic or diverticulitis

## Allergic Rhinitis

- see Otolaryngology, OT23

### Definition
- inflammation of the nasal mucosa that is triggered by an allergic reaction
- classification
  - seasonal
    - symptoms during a specific time of the year
    - common allergens: trees, grass and weed pollens, airborne moulds
  - perennial
    - symptoms throughout the year with variation in severity
    - common allergens: dust mites, animal dander, moulds
- persistent allergic rhinitis may lead to chronic rhinosinusitis

**Differential Diagnosis**
- Acute viral infection
- Vasomotor rhinitis
- Deviated septum
- Nasal polyps
- Acute/chronic sinusitis
- Drug-induced rhinitis

**Rhinitis Medicamentosa**
Rebound nasal congestion. Occurs with prolonged use (>5-7 d) of vasoconstrictive intranasal medications. Patient may become dependent, requiring more frequent dosing to achieve the same decongestant effect

### Epidemiology
- affects approximately 40% of children and 20-30% of adults
- prevalence has increased in developed countries, particularly in the past two decades
- associated with asthma, eczema, sinusitis, and otitis media

### Etiology
- increased IgE levels to certain allergens → excessive degranulation of mast cells → release of inflammatory mediators (e.g. histamine) and cytokines → local inflammatory reaction

### Assessment
- identify allergens
- take an environmental/occupational history
- ask about related conditions (e.g. atopic dermatitis, asthma, sinusitis, and family history)

### Management
- conservative
  - minimize exposure to allergens
    - most important aspect of management, often sufficient (may take months)
  - maintain hygiene, saline nasal rinses
- pharmacologic agents
  - oral antihistamines – first line therapy for mild symptoms
    - e.g. cetirizine (Reactine®), fexofenadine (Allegra®), loratadine (Claritin®)
  - intranasal corticosteroids for moderate/severe or persistent symptoms (>1 mo of consistent use to see results)
  - intranasal decongestants (use must be limited to <5 d to avoid rhinitis medicamentosa)

- allergy skin testing
  - for patients with chronic rhinitis whose symptoms are not controlled by conservative and pharmacological therapy
  - may identify allergens to include in immunotherapy treatment
- immunotherapy (allergy shots)
  - reserved for severe cases unresponsive to pharmacologic agents
  - consists of periodic (usually weekly) subcutaneous injections of custom prepared solutions of one or more antigens to which the patient is allergic

# Amenorrhea

- see Gynecology, GY7

# Anxiety

- see Psychiatry, PS20

## Epidemiology

- 25-30% of patients in primary care settings have psychiatric disorders
- many are undiagnosed or untreated; hence the need for good screening
- high rate of coexistence of anxiety disorders and depression

## Screening

- screening tools such as the Generalized Anxiety Disorder 7-item (GAD-7) tool
- screening questions
  - Do you tend to be an anxious or nervous person?
  - Have you felt unusually worried about things recently?
  - Has this worrying affected your life? How?

## Assessment

- associated symptoms
- risk factors: past history of anxiety, stressful life event, trauma, social isolation, female, comorbid psychiatric diagnosis (e.g. depression), family history of anxiety or depression
- assess substance abuse, suicidal ideation/self-harm
- to differentiate anxiety disorders, consider symptoms and their duration
- use the GAD-7 tool to assess and monitor levels of anxiety

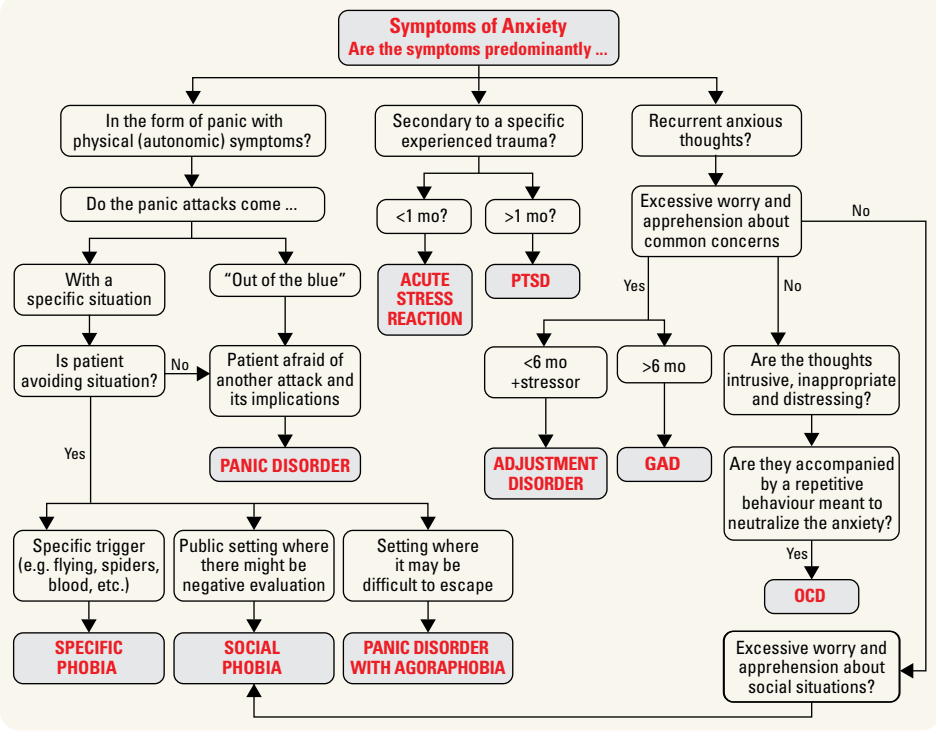



**Figure 7. Differentiating anxiety disorders**
Adapted from: Evans M, Bradwejn J, Dunn L. Anxiety Review Panel. Guidelines for the treatment of anxiety disorders in primary care. Toronto: Queen's Printer of Ontario, 2000.41

**Symptoms of GAD**

**AND I C REST**
**A**nxious, nervous, or worried
**N**o control over the worry
**D**uration >6 mo
**I**rritability
**C**oncentration impairment
**R**estlessness
**E**nergy decreased
**S**leep impairment
**T**ension in muscles
Can Fam Physician 2005;51:1340-42

**Differential Diagnosis of Anxiety Disorders**
- Panic disorder
- GAD
- Social Anxiety Disorder (previously Social Phobia)
- Agoraphobia
- Specific phobia
- Selective Mutism
- Separation Anxiety Disorder
- Other: GMC, AMC, mood disorder, psychotic disorder, OCD, PTSD

**Rule Out**
- Cardiac (post MI, arrhythmias)
- Endocrine (hyperthyroidism, diabetes, pheochromocytoma)
- Respiratory (asthma, COPD)
- Somatoform disorders
- Psychotic disorders
- Mood disorders (depression, bipolar)
- Personality disorder (OCPD)
- Drugs (amphetamines, thyroid preparations, caffeine, OTC for colds/decongestants, alcohol/benzodiazepine withdrawal)

### Management
- patient education: emphasize prevalence, good recovery rate of anxiety conditions
- lifestyle advice: exercise, decrease caffeine and alcohol intake
- psychological: CBT, including exposure therapy, relaxation techniques, and mindfulness strategies
- pharmacotherapy: see Psychiatry, PS43
- provide self-help materials, connect with community resources (e.g. support groups), and provide support to family and caregivers

## Asthma/COPD

- see Respirology, R7

### Definition
- asthma
  - chronic, reversible airway inflammation characterized by periodic attacks of wheezing, SOB, chest tightness, and coughing
  - airways are hyper-responsive to triggers/antigens leading to acute obstructive symptoms by bronchoconstriction, mucous plugs, and increased inflammation
  - cannot be diagnosed at first presentation; is called reactive airway disease until recurrent presentations
  - PFTs can be done starting at age 6 or when child is able to follow testing instructions
  - peak flow metres are useful in the office and at home for monitoring
- chronic obstructive pulmonary disease (COPD)
  - group of chronic, progressive, non-reversible lung diseases characterized by limited airflow with variable degrees of air sac enlargement and lung tissue destruction
  - emphysema and chronic bronchitis are the most common forms

**Table 8. Differentiating COPD from Asthma**

| | COPD | Asthma |
|---|---|---|
| **Age of Onset** | Usually in 6th decade | Any age (but 50% of cases are diagnosed in children age <10) |
| **Role of Smoking** | >10 pack yr | Not causal, known trigger |
| **Reversibility of Airflow Obstruction** | Airflow obstruction is chronic and persistent | Airflow obstruction is episodic and usually reversible with therapy |
| **Evolution** | Slow, progressive worsening (with periodic exacerbations) | Stable, episodic, <50% will outgrow |
| **History of Allergy** | Infrequent | >50% patients |
| **Precipitators** | Environmental irritants (air pollution), cigarette smoking, α-1 antitrypsin deficiency, viral infection, occupational exposure (firefighters, dusty jobs) | Environmental irritants (dust, pollen), animal fur, cold air, exercise, URTIs, cigarette smoke, use of β-blockers/ASA |
| **Symptoms/Signs** | Chronic cough, sputum, and/or dyspnea | Wheeze (hallmark symptom), dyspnea, chest tightness, prolonged expiration, cough which is worse in the cold, at night, and in the early AM |
| **Diffusion Capacity** | Decreased (more so in pure emphysema) | Normal (for pure asthma) |
| **Hypoxemia** | Chronic in advanced stages | Not usually present<br>Episodic with severe attacks |
| **Spirometry** | May have improvement with bronchodilators but not universally seen | Marked improvement with bronchodilators or steroids |
| **Chest X-Ray** | Often normal<br>Increased bronchial markings (chronic bronchitis) and chronic hyperinflation (emphysema) often co-exist, bullae | Often normal or episodic hyperinflation<br>Hyperinflation during asthma attack |
| **Management** | **Mild**<br>Step 1: SABA prn (salbutamol)<br>Step 2: SABA prn + LAAC (i.e. tiotropium) or + LABA (e.g. salmeterol)<br>**Moderate**<br>Step 3: SABA prn + LAAC + low-dose combined ICS/LABA; consider inhaled vs. oral steroids<br>**Severe**<br>Step 4: ± theophylline<br>Pneumococcal vaccination, annual influenza immunization | Ongoing patient education, and environmental control<br>SABA taken prn as rescue medication + maintenance meds<br>Maintenance medications<br>Step 1: Low-dose ICS<br>Step 2: Medium/high-dose ICS or low-dose ICS plus either LABA, LT modifier, or long-acting theophylline<br>Step 3: Medium/high-dose ICS + either LABA, LT modifier, or long-acting theophylline<br>Step 4: As above + immunotherapy ± oral glucocorticosteroids + pneumococcal vaccination, annual influenza immunization |

ICS = inhaled corticosteroids; LAAC = long-acting anticholinergic; LABA = long-acting β-agonist; LT modifier = leukotriene modifier; SABA = short-acting β-agonist

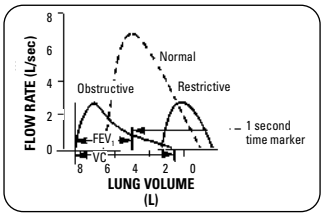



**Figure 8. Expiratory flow volume curves** (obstructive, normal, and restrictive disease)
See Respirology, R4 Adapted from: Weinberger SE. Principles of pulmonary medicine, 5th ed. With permission from Elsevier. ©2008

**Signs of Poorly Controlled Asthma**
- $\beta_2$-agonist use >4x/wk
- Asthma-related absence from work/school
- Exercise induced asthma
- Night-time symptoms >1x/wk

**What Colour is Your Inhaler?**

| Name | Body/Cap Colour |
|---|---|
| **$\beta_2$-Agonists** | |
| salbutamol – Ventolin® | light blue/navy |
| salmeterol – Serevent® | teal/light teal |
| terbutaline – Bricanyl® | blue/white |
| **ICS** | |
| fluticasone – Flovent® | orange/peach |
| budesonide – Pulmicort® | white/brown |
| **Combined Long-Acting $\beta_2$-Agonist + ICS** | |
| fluticasone/salmeterol – Advair® | purple discus |
| budesonide/formoterol – Symbicort® | red/white |
| ipratropium/albuterol – Combivent® | clear/orange |
| **Anticholinergics** | |
| ipratropium – Atrovent® | clear/green |
| tiotropium – Spiriva® | white/turquoise |

**More About Inhalers**
- Aerosols (puffers=MDI, MDI + spacer) MDIs should be used with spacers to:
  - Reduce side effects
  - Improve amount inhaled
  - Increase efficiency of use
- Dry Powder Inhalers (discus, turbuhaler, and diskhaler) require deep and fast breathing (may not be ideal for children)
- Nebulizers can be used to convert liquid medications into a fine mist: recommended for use if contraindications to MDIs

**Differential Diagnosis of Wheezing**
- Allergies, anaphylaxis
- Asthma, reactive airway disease
- GERD
- Infections (bronchitis, pneumonia)
- Obstructive Sleep Apnea
- COPD
- Less common: congestive heart disease, foreign body, malignancy, cystic fibrosis, vocal cord dysfunction

When prescribing salbutamol, watch out for signs of **hypokalemia**: lethargy, irritability, paresthesias, myalgias, weakness, palpitations, N/V, polyuria

# Benign Prostatic Hyperplasia

• see Urology, U7

## Definition
• hyperplasia of the stroma and epithelium in the periurethral transition zone

## History and Physical
• include current/past health, surgeries, trauma, current medications including OTC
• specific urinary symptoms
• physical exam must include DRE for size, symmetry, nodularity, and texture of prostate (prostate is symmetrically enlarged, smooth, and rubbery in BPH)

## Investigations
• urinalysis to exclude UTI and for microscopic hematuria (common sign)
• serum PSA: protein produced by prostatic tissue
  ▪ values
    ◆ <4.0 ng/mL: normal, but must take into account patient's age and velocity of PSA increase
    ◆ 4-10 ng/mL: consider measuring free/total PSA
    ◆ >10 ng/mL: high likelihood of prostate pathology
  ▪ PSA testing is inappropriate in men with a life expectancy less than 10 yr or patients with prostatitis, UTI
  ▪ increased PSA in a younger man is more often due to cancer than other causes
  ▪ abnormal DRE or PSA should trigger further assessment
  ▪ discuss test with men at increased risk of prostate cancer (FHx, African ancestry) or who are concerned about development of prostate cancer
  ▪ decision to test PSA in an asymptomatic man should involve discussion about the risks and possible benefits
• other tests
  ▪ Cr, BUN, post-void residual volume by ultrasound, urodynamic studies, renal ultrasound, patient voiding diary
• tests NOT recommended as part of routine initial evaluation include:
  ▪ cystoscopy, cytology, prostate ultrasound or biopsy, IVP, urodynamic studies

**Table 9. Symptoms and Complications of BPH**

| Obstructive Symptoms | Irritative Symptoms | Late Complications |
|---|---|---|
| Hesitancy (difficulty starting urine flow)<br>Diminution in size and force of urinary stream<br>Stream interruption (double voiding)<br>Urinary retention (bladder does not feel completely empty)<br>Post-void dribbling<br>Overflow incontinence<br>Nocturia | Urgency<br>Frequency<br>Nocturia<br>Urge incontinence<br>Dysuria | Hydronephrosis<br>Loss of renal concentrating ability<br>Systemic acidosis<br>Renal failure |

## Management
• referral to urologist if moderate/severe symptoms
• conservative: for patients with mild symptoms or moderate/severe symptoms considered by the patient to be non-bothersome
  ▪ fluid restriction (avoid alcohol and caffeine)
  ▪ avoidance/monitoring of certain medications (e.g. antihistamines, diuretics, antidepressants, decongestants)
  ▪ pelvic floor/Kegel exercises
  ▪ bladder retraining (scheduled voiding)
• pharmacological: for moderate/severe symptoms
  ▪ α-receptor antagonists (e.g. terazosin [Hytrin®], doxazosin [Cardura®], tamsulosin [Flomax®], alfuzosin [Xatral®])
    ◆ relax smooth muscle around the prostate and bladder neck
  ▪ 5-α reductase inhibitors (e.g. finasteride [Proscar®])
    ◆ only for patients with demonstrated prostatic enlargement due to BPH
    ◆ inhibit the enzyme responsible for conversion of testosterone to dihydrotestosterone (DHT) thus reducing growth of prostate
  ▪ phytotherapy (e.g. saw palmetto berry extract, Pygeum africanum)
    ◆ more studies are required before it can be recommended as standard therapy (currently considered safe)
• surgical
  ▪ TURP (transurethral resection of the prostate), TUIP (transurethral incision of the prostate, for prostate <30 g)
  ▪ absolute indications: failed medical therapy, intractable urinary retention, benign prostatic obstruction leading to renal insufficiency
  ▪ complications: impotence, incontinence, ejaculatory difficulties (retrograde ejaculation), decreased libido



**Self-Management Asthma and COPD Education and Written Action Plan**
• Education is a key component in management of asthma and COPD
• Guided self-management combining education, regular medical review, self-assessment, and written action plan have been shown to reduce hospitalizations, ER visits, and missed days at work or school.
• Sample action plans available online: http://www.respiratoryguidelines.ca



**Differential Diagnosis**
• Prostate cancer
• Urethral obstruction
• Bladder neck obstruction
• Neurogenic bladder
• Overactive bladder
• Cystitis
• Prostatitis

# Bronchitis (Acute)

## Definition
- acute infection of the tracheobronchial tree causing inflammation leading to bronchial edema and mucus formation

## Epidemiology
- 5th most common diagnosis in family medicine, and most common is URTI

## Etiology
- 80% viral: rhinovirus, coronavirus, adenovirus, influenza, parainfluenza, and respiratory syncytial virus (RSV)
- 20% bacterial: *M. pneumoniae, C. pneumoniae, S. pneumoniae*

## Investigations
- acute bronchitis is typically a clinical diagnosis
- sputum culture/Gram stain is not useful
- CXR if suspect pneumonia (cough >3 wk, abnormal vital signs, localized chest findings) or CHF
- PFT with methacholine challenge if suspect asthma

## Management
- primary prevention: frequent hand washing, smoking cessation, avoid irritant exposure
- symptomatic relief: rest, fluids (3-4 L/d when febrile), humidity, analgesics, and antitussives as required
- bronchodilators may offer improvement of symptoms (e.g. salbutamol)
- current literature does not support routine antibiotic treatment for the management of acute bronchitis because it is most likely to be caused by a viral infection
  - antibiotics may be useful if elderly, comorbidities, suspected pneumonia, or if the patient is toxic (see *Antimicrobial Quick Reference*, FM51)
  - antibiotics in children show no benefit

**Differential Diagnosis of Bronchitis**
- URTI
- Asthma
- Acute exacerbation of chronic bronchitis
- Sinusitis
- Pneumonia
- Bronchiolitis
- Pertussis
- Environmental/occupational exposures
- Post-nasal drip
- Others: GERD, CHF, cancer, aspiration syndromes, CF, foreign body

**How to Tell if Viral or Bacterial?**
Bacterial infections tend to give a higher fever, excessive amounts of purulent sputum production, and may be associated with concomitant COPD

# Chest Pain

- see Cardiology and Cardiac Surgery, C4 and Emergency Medicine, ER21

## Differential Diagnosis

**Table 10. Differential Diagnosis of Chest Pain**

| Diagnosis | Clinical Findings | LR+ | LR– |
|---|---|---|---|
| **Acute Myocardial Infarction** | Chest pain radiates to both arms | 7.1 | 0.67 |
| | Third heart sound on auscultation | 3.2 | 0.88 |
| | Hypotension | 3.1 | 0.96 |
| **Chest Wall Pain** | >2 of: localized muscle tension; stinging pain; pain reproducible by palpation; absence of cough | 3.0 | 0.47 |
| **Gastroesophageal Reflux Disease** | Burning retrosternal pain, acid regurgitation, sour or bitter taste in the mouth; 1 wk trial of high-dose proton pump inhibitor relieves symptoms | 3.1 | 0.30 |
| **Panic Disorder/Anxiety State** | Single question: In the past 4 wk, have you had an anxiety attack (suddenly feeling fear or panic)? | 4.2 | 0.09 |
| **Pericarditis** | Clinical triad of pleuritic chest pain (increases with inspiration or when reclining, and is lessened by leaning forward), pericardial friction rub, and electrocardiographic changes (diffuse ST segment elevation and PR interval depression without T wave inversion) | N/A | N/A |
| **Pneumonia** | Egophony | 8.6 | 0.96 |
| | Dullness to percussion | 4.3 | 0.79 |
| | Fever | 2.1 | 0.71 |
| | Clinical impression | 2.0 | 0.24 |
| **Heart Failure** | Pulmonary edema on chest radiography | 11.0 | 0.48 |
| | Clinical impression/judgment | 9.9 | 0.65 |
| | History of heart failure | 5.8 | 0.45 |
| | History of acute myocardial infarction | 3.1 | 0.69 |
| **Pulmonary Embolism** | High pretest probability based on Wells criteria | 6.8 | 1.8 |
| | Moderate pretest probability based on Wells criteria | 1.3 | 0.7 |
| | Low pretest probability based on Wells criteria | 0.1 | 7.6 |
| **Acute Thoracic Aortic Dissection** | Acute chest or back pain and a pulse differential in the upper extremities | 5.3 | N/A |

Adapted from: McConaghy J, Rupal S. Outpatient diagnosis of acute chest pain in adults. Am Fam Physician. 2013 Feb 1; 87(3): 177.182

**Risk Factors for CAD**

**Major**
- Smoking
- Diabetes
- HTN
- Hyperlipidemia
- Family history of early CAD in first degree relative (males <55 yr, females <65 yr)
- Untreated obstructive sleep apnea
- Chronic kidney disease

**Minor**
- Obesity
- Sedentary lifestyle
- Age

**Red Flags**
- Severe pain
- Pain for >20 min
- New onset pain at rest
- Severe SOB
- Loss of consciousness
- Hypotension
- Tachycardia
- Bradycardia
- Cyanosis

**Ruling Out Coronary Artery Disease in Primary Care**
CMAJ 2010;182(12):1295-1300
Components of the prediction rule used to determine the presence or absence of CAD in patients with chest pain in primary care:
- Age/sex (female ≥65, male ≥55): 1 pt
- Known clinical vascular disease (coronary artery disease, occlusive vascular disease, or cerebrovascular disease): 1 pt
- Pain worse during exercise: 1 pt
- Pain not reproducible by palpation: 1 pt
- Patient assumes pain is of cardiac origin: 1 pt

Positive result: 3-5 pts; negative result: ≤2 pts (sensitivity: 87.1%, specificity: 80%)

### Investigations
- ECG, CXR, and others if indicated (cardiac enzymes, d-dimers, liver function tests, etc.)
- refer to ED if suspect serious etiology (e.g. aortic dissection, MI)

### Management of Common Causes of Chest Pain
- angina/ischemic heart disease
  - nitroglycerin (NTG): wait 5 min between sprays and if no effect after 3 sprays, send to ED
- myocardial infarction
  - ASA (160-325 mg, chewed stat), clopidogrel (Plavix®), LMWH (enoxaparin), morphine, oxygen, NTG
  - ± reperfusion therapy with fibrinolytics (e.g. tissue plasminogen activator (tPA), reteplase (rPA), tenecteplase (TNK), or streptokinase (SK)) if within 12 h (ideally <30 min) or percutaneous intervention (cath lab) if <90 min
  - start β-blocker (e.g. metoprolol starting dose 25 mg PO q6h or bid, titrating to HR goal of 55-60 bpm)
- endocarditis: antibiotic choice is based on whether patient has a native or prosthetic heart valve as well as culture and sensitivity results
- GERD: antacids, H2-blockers, PPIs, patient education
- costochondritis: NSAIDs

**MI in Elderly Women**
Elderly women can often present with dizziness, back pain, lightheadedness, or weakness in the absence of chest pain

**MI in Diabetics**
May present with dyspnea, syncope, and fatigue in the absence of chest pain

# Common Cold (Acute Rhinitis)

- see Infectious Diseases, *Pneumonia and Influenza*, ID7

### Definition
- viral URTI with inflammation

### Epidemiology
- most common diagnosis in family medicine, peaks in winter months
- incidence: adults = 2-4/yr, children = 6-10/yr
- organisms
  - mainly rhinoviruses (30-35% of all colds)
  - others: coronavirus, adenovirus, RSV, influenza, parainfluenza, coxsackie virus
- incubation: 1-5 d
- transmission: person-person contact via secretions on skin/objects and by aerosol droplets

### Risk Factors
- psychological stress, excessive fatigue, allergic nasopharyngeal disorders, smoking, sick contacts

### Clinical Features
- symptoms
  - local: nasal congestion, clear to mucopurulent secretions, sneezing, sore throat, conjunctivitis, cough
  - general: malaise, headache, myalgias, mild fever
- signs
  - erythematous nasal/oropharyngeal mucosa, enlarged lymph nodes
  - normal chest exam
- complications
  - secondary bacterial infection: otitis media, sinusitis, bronchitis, pneumonia
  - asthma/COPD exacerbation

### Differential Diagnosis
- allergic rhinitis, pharyngitis, influenza, laryngitis, croup, sinusitis, bacterial infections

### Management
- patient education
  - symptoms peak at 1-3 d and usually subside within 1 wk
  - cough may persist for days to weeks after other symptoms disappear
  - no antibiotics indicated because of viral etiology
  - secondary bacterial infection can present within 3-10 d after onset of cold symptoms
- prevention
  - frequent hand washing, avoidance of hand to mucous membrane contact, use of surface disinfectant
  - yearly influenza vaccination
- symptomatic relief
  - rest, hydration, gargling warm salt water, steam, nasal irrigation (spray/pot)
  - analgesics and antipyretics: acetaminophen, ASA (not in children because risk of Reye's syndrome), ibuprofen
  - cough suppression: dextromethorphan or codeine if necessary (children <6 yr of age should not use any cough/cold medications)
  - decongestants, antihistamines
- patients with reactive airway disease will require increased use of bronchodilators and inhaled steroids

**Influenza vs. Colds: A Guide to Symptoms**

| Features | Flu | Cold |
|---|---|---|
| Onset of illness | Sudden | Slow |
| Fever | High fever | None |
| Exhaustion level | Severe | Mild |
| Cough | Dry severe or hacking | ± |
| Throat | Fine | Sore |
| Nose | Dry and clear | Runny |
| Head | Achy | Headache-free |
| Appetite | Decreased | Normal |
| Muscles | Achy | Fine |
| Chills | Yes | No |

**Echinacea for Preventing and Treating the Common Cold**
Cochrane DB Syst Rev 2014;2:CD000530
**Purpose**: To assess whether Echinacea preparations are effective and safe for the prevention and treatment of the common cold.
**Methods**: Meta-analysis of RCTs comparing mono-preparations of Echinacea with placebo. Primary efficacy outcome was number of individuals with at least one cold in prevention trials, and duration of colds in treatment trials. Primary safety and acceptability outcome was number of participants dropping out due to adverse events.
**Results**: 24 double-blind trials with 4631 participants were included. No prevention study comparisons comparing Echinacea and placebo found a statistically significant difference in terms of number of patients with at least one cold episode, though a relative risk reduction of 10% to 20% was identified. Of treatment trials reporting on duration of colds, only 1 study of 7 showed a significant effect favouring Echinacea over placebo. No significant differences were found between Echinacea and placebo groups in number of dropouts due to adverse events, though prevention trials showed a trend towards higher dropout numbers due to adverse events in treatment groups.
**Conclusions**: Echinacea products have not been shown to provide benefits for treating colds, although it is possible there is a weak benefit from some Echinacea products. Individual prophylaxis trials consistently show positive (if non-significant) trends, although potential effects are of questionable clinical relevance.

# Concussion/Mild Traumatic Brain Injury

- see Neurosurgery, NS31 and Emergency Medicine, ER8
- a useful tool for the assessment of individuals and athletes with concussion is the Sport Concussion Assessment Tool, 5th edition (SCAT5), Br J Sports Med 2017;0:1-8

# Contraception

- see Gynecology, GY15

### EMERGENCY CONTRACEPTION

- hormonal EC (Yuzpe® or Plan B®, usually 2 doses taken 12 h apart) or post-coital copper IUD insertion
- hormonal EC is effective if taken within 72 h of unprotected intercourse (reduces chance of pregnancy by 75-85%), most effective if taken within 24 h, does not affect an established pregnancy
- copper IUDs inserted within 5 d of unprotected intercourse are significantly more effective than hormonal EC (reduces chance of pregnancy by ~99%)
- pregnancy test should be performed if no menstrual bleeding within 21 d of either treatment
- advance provision of hormonal EC increases the use of EC without decreasing the use of regular contraception
- pharmacists across Canada can dispense Plan B® OTC

# Cough

### History and Physical

- duration (chronic - 8 wk), onset, frequency, quality (dry vs. productive), sputum characteristics, provoking/relieving factors, recent changes
- associated symptoms: fever, dyspnea, hemoptysis, wheezing, chest pain, orthopnea, PND, rhinitis, reflux, post-nasal drip
- constitutional symptoms: fever, chills, fatigue, night sweats
- risk factors: smoking, occupation, exposure, family history of lung CA or other CA, TB status, recent travel
- medications (e.g. ACEI, β-blockers), allergies
- PMH: lung (asthma, COPD, CF), heart (CHF, MI, arrhythmias), chronic illness, GI (reflux)
- vitals including $O_2$ saturation, respiratory exam, HEENT and precordial exam

### Investigations

- guided by findings on history and physical
  - consider throat swab, CXR, PFTs, upper GI series, sputum culture test for acid-fast bacilli (if TB is suspected)

**Differential Diagnosis**

**Common Causes**
- Upper airway cough syndrome (post-nasal drip)
- Asthma/COPD
- GERD
- Non-asthmatic eosinophilic bronchitis

**Other Causes**
- ACEI
- Aspiration
- Bronchiectasis
- Cystic fibrosis
- Chronic interstitial lung disease
- CHF
- Lung/laryngeal cancer
- Pertussis
- Psychogenic
- Restrictive lung disease
- TB, atypical mycobacterium, and other chronic lung infections

# Dementia (Major Neurocognitive Disorder)

- see Psychiatry, PS23

### Epidemiology

- 15% of Canadians ≥65 yr are living with dementia; risk for dementia doubles every 5 yr after age 65
- prevalence of depression in dementia is 20-60%; major depression decreases as dementia severity increases; vascular and mixed dementias have a higher prevalence of depression
- leading types of dementia: Alzheimer's (40-50%), Mixed (20-25%), Lewy-Body (5-15%), Vascular (5-10%), Frontotemporal (5-10%)

### Investigations

- history, physical exam, MMSE, MOCA (best screening test), Dementia Quick Screen (see sidebar)
- investigations are completed to exclude reversible causes of dementia and should be selected based on the clinical circumstances
- CBC, liver enzymes, TSH, renal function tests, serum electrolytes, serum calcium, serum glucose, vitamin $B_{12}$, folate, VDRL, HIV, head CT

### Management

- treat and prevent reversible causes
- provide orientation cues (e.g. calendars, clocks) and optimize vision and hearing
- family education, counselling, and support (respite programs, group homes)
- pharmacologic therapy: N-methyl-d-aspartate receptor antagonists and cholinesterase inhibitors slow rate of cognitive decline; low-dose neuroleptics and antidepressants can be used to treat behavioural and emotional symptoms
- 20% of patients develop clinical depression, most commonly seen in vascular dementia

**Dementia Quick Screen = Mini Cog + Animal Naming**
- 3 simple tests, takes about 2 min
- Use when suspect mild cognitive impairment or when patient is at high risk
- Mini Cog = 3 words recalled + clock drawing
  - Clock Drawing – including numbers and hands so time shows 10 min past 11 (normal = correct number/hand placing or only minor spacing problems)
  - 0 word recall = impairment
  - 1-2 words and clock drawing abnormal = impairment
  - 3 words recalled = normal
  - Naming animals in 1 min (normal = >15 in one min)
- Interpretation: If all 3 results within normal range, cognitive impairment unlikely
- Return for further evaluation if:
  - <15 animals named
  - 0-1 words recalled
  - Clock drawing abnormal

# Depression

• see Psychiatry, PS12

## Etiology
- often presents as non-specific complaints (e.g. sleep disturbance, chronic fatigue, pain)
- depression is a clinical diagnosis and tests are done in order to rule out other causes of symptoms
- 2/3 of patients may not receive appropriate treatment for their depression
- early diagnosis and treatment improve outcomes

## Screening Questions
- Canadian Task Force on Preventive Health Care (2013) recommends not routinely screening for depression
- if screening indicated, use the Patient Health Questionnaire (PHQ-2)
  - "Over the past 2 wk, how often have you been bothered by any of the following problems?":
    - little interest or pleasure in doing things
    - feeling down, depressed, or hopeless
- the PHQ-2 is scored out of 6, with a score of 3 or more considered positive
  - those who screen positive should be evaluated with the PHQ-9 to determine whether they meet criteria for depression
- PHQ-9 tool is useful to diagnose and monitor depression; use Geriatric Depression Scale (GDS) for the geriatric population

## Assessment
- risk factors: see Psychiatry, PS12
- personal or family history of depression
- medications and potential substance abuse problems
- high risk for suicide/homicide
  - fill out Form 1 (in Ontario): application by physician to hospitalize a patient against his/her will for psychiatric assessment (up to 72 h)
- functional impairment (e.g. work, relationships)
- at least 5 out of 9 criteria including at least one of anhedonia or depressed mood ≥2 wk for actual diagnosis to be met (see sidebar)
- validated depression rating scales: Beck's Depression Inventory, Zung's self-rating depression scale, Children's Depression Inventory, Geriatric Depression Scale, Personal Health Questionnaire Depression Scale (PHQ-9)
- routine medical workup (physical exam, CBC, TSH, ferritin, folate, $B_{12}$, electrolytes, urinalysis, glucose, etc.)

## Treatment
- goal: full remission of symptoms and return to baseline psychosocial function
- phases of treatment
  - acute phase (8-12 wk): relieve symptoms and improve quality of life
  - maintenance phase (6-12 mo after symptom resolution): prevent relapse/recurrence, must stress importance of continuing medication treatment for full duration to patients
- treatment options are pharmacotherapy, psychotherapy, or a combination of both
  - combination therapy is synergistic and most effective (refer to EBM in sidebar)
- treatment of youth (age 10-21)
  - for mild depression, a period of active support and monitoring before initiating treatment is recommended
  - fluoxetine is first line among SSRIs (most evidence)
    - monitor closely for adverse effects such as suicidal ideation and behaviour
  - psychotherapy
    - CBT or interpersonal therapy (IPT) alone can be used for mild depression
    - psychotherapy plus medication is recommended for moderate to severe depression
  - treatment should continue for at least 6 mo
    - ongoing management should include assessment in key domains (school, home, social setting)
    - reassessment and referral is recommended if there is no improvement after 6-8 wk of treatment
    - consider referral for adolescents with moderate/severe depression and coexisting psychosis and/or substance abuse

**Table 11. Common Medications**

| Class | Examples | Action | Side Effects | Notes |
|---|---|---|---|---|
| **SSRI** | paroxetine (Paxil®)<br>fluoxetine (Prozac®)<br>sertraline (Zoloft®)<br>citalopram (Celexa®)<br>fluvoxamine (Luvox®)<br>escitalopram (Cipralex®) | Block serotonin reuptake | Sexual dysfunction (impotence, decreased libido, delayed ejaculation, anorgasmia), headache, GI upset, weight loss, tremors, insomnia, fatigue, increase QT interval (baseline ECG is suggested) | First line therapy for youth is fluoxetine; paroxetine is not recommended for youth (controversial) |
| **SNRI** | venlafaxine (Effexor®)<br>duloxetine (Cymbalta®) | Block serotonin and norepinephrine reuptake | Insomnia, tremors, tachycardia, sweating | |
| **SDRI** | bupropion (Wellbutrin®) | Block dopamine and NE reuptake | Headache, insomnia, nightmares, seizures, less sexual dysfunction than SSRIs | Often chosen for lack of sexual side effects, can be used for augmentation of anti-depressant effects with other classes of medication |
| **TCA** | amitriptyline (Elavil®) | Block serotonin and NE reuptake | Sexual dysfunction, weight gain, tremors, tachycardia, sweating | Narrow therapeutic window, lethal in overdose |

**Must Ask About/Rule Out**
- Suicidal/homicidal ideation
- Psychosis
- Substance use/abuse/withdrawal
- Anxiety
- Bipolar/manic/hypomanic episodes
- Bereavement
- Intimate partner violence
- Post-partum depression
- Organic cause

**Differential Diagnosis**
- Other psychiatric disorders (e.g. anxiety, personality, bipolar, adjustment disorder, schizoaffective, seasonal affective disorder, substance abuse/withdrawal)
- Cancer (50% of patients with tumours, especially of brain, lung, and pancreas, develop symptoms of depression before the diagnosis of cancer is made)
- Chronic fatigue syndrome
- Early dementia
- Endocrine (e.g. hyper/hypothyroidism, DM, adrenal disorders)
- Infections (mononucleosis)
- Liver failure, renal failure
- Medication side effects (β-blockers, benzodiazepines, glucocorticoids, interferon)
- Menopause
- Neurological (Parkinson's, MS)
- Vitamin deficiency (pernicious anemia, pellagra)

**Criteria for Depression (≥5/9 with at least one of anhedonia or depressed mood for ≥2 wk)**

**M-SIGECAPS**
**M** Depressed **M**ood
**S** Increased/decreased **S**leep
**I** Decreased **I**nterest
**G** **G**uilt
**E** Decreased **E**nergy
**C** Decreased **C**oncentration
**A** Increased/decreased **A**ppetite and weight
**P** **P**sychomotor agitation/retardation
**S** **S**uicidal ideation

**Combined Pharmacotherapy and Psychological Treatment for Depression: A Systematic Review**
Arch Gen Psychiatry 2004;61:714-719
**Purpose**: To examine the relationship between adherence and efficacy of antidepressant medications plus psychological treatment versus medications alone in the management of depressive disorders.
**Methods**: Systematic review of RCTs comparing antidepressant medications alone versus combination therapy with psychological intervention included. Efficacy and adherence to therapy were the main outcomes.
**Results**: 16 trials with 1842 patients were included. Patients receiving combination therapy showed significantly greater improvements than those receiving medications alone (odds ratio (OR) 1.86, 95% CI 1.38-2.52); dropout and non-responder proportions did not differ in distribution between the two groups (OR 0.86, 0.60-1.24). A significant advantage with combination therapy was noted in studies with follow-up longer than 12 wk (OR 2.21, 1.22-4.03), accompanied by significant reduction in dropout and non-responder proportions.
**Conclusion**: Combination therapy with psychological treatment and medication is associated with greater improvement rates than medication alone, and may decrease dropout rates with longer therapies.

### Prognosis
- up to 40% resolve spontaneously within 6-12 mo
- risks of recurrence: 50% after 1 episode; 70% after 2 episodes; 90% after 3 episodes

# Diabetes Mellitus

- see Endocrinology, E7
- see 2013 Clinical Practice Guidelines from Canadian Diabetes Association (updated in 2016), available from: http://guidelines.diabetes.ca/fullguidelines
- see Diabetes Mellitus Patient Care Flow Sheet from Canadian Diabetes associated, available from: http://guidelines.diabetes.ca/organizingcare/patientcareflowsheet

### Definition
- metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both

### Classification and Diagnosis
- see Endocrinology, E7

### Epidemiology
- major health concern, affecting up to 10% of Canadians
- incidence of type 2 DM is rising due to increasing obesity, sedentary lifestyle, and age of the population
- leading cause of new-onset blindness and renal dysfunction
- Canadian adults with DM are twice as likely to die prematurely compared to persons without DM

### Risk Factors
- type 1 DM
  - personal or family history of autoimmune disease
- type 2 DM
  - first degree relative with DM
  - age ≥40 yr
  - obesity (especially abdominal), HTN, hyperlipidemia, CAD, vascular disease
  - prior gestational diabetes mellitus, macrosomic baby (>4 kg)
  - PCOS
  - history of IGT or IFG
  - presence of complications associated with DM
  - presence of associated diseases: PCOS, acanthosis nigricans, psychiatric disorders, HIV
  - medications: glucocorticoids, atypical antipsychotics, HAART
- both
  - member of a high risk population (e.g. Aboriginal, Hispanic, Asian, or African descent)

### Screening
- type 2 DM
  - FBG or HbA1c in everyone ≥40 q3yr, or at high risk using the CANRISK calculator
  - more frequent and/or earlier testing if presence of ≥1 risk factor (see above)
- gestational diabetes mellitus (see Obstetrics, OB26)
  - all pregnant women between 24-28 wk gestation

### Goals of Therapy
- see Endocrinology and side bar (SMART Goals)

**DM Related Symptoms**

**Hyperglycemia:** polyphagia, polydipsia, polyuria, weight change, blurry vision, yeast infections

**Diabetic Ketoacidosis (DKA):** fruity breath, anorexia, N/V, fatigue, abdominal pain, Kussmaul breathing, dehydration

**Hypoglycemia:** hunger, anxiety, tremors, palpitations, sweating, headache, fatigue, confusion, seizures, coma

**Long-Term Complications of DM**
- Microvascular: nephropathy, retinopathy, neuropathy
- Macrovascular: CAD, CVD, PVD

**Smart Goals**
**Diabetes Quick Reference Guide**

**A** A1C: Optimal Glycemic Control (Usually <7%)
**B** BP: Optimal Blood Pressure Control (≤130/80)
**C** Cholesterol: LDL-C <2 if treating
**D** Drugs: Consider ACEI/ARB, Statin, and ASA
**E** Exercise/Eating
**S** Smoking Cessation

## Assessment and Monitoring

### Table 12. Assessment and Monitoring

| | Initial Assessment | q2-4mo | Annually |
|---|---|---|---|
| **History** | Symptoms of hyperglycemia, ketoacidosis, hypoglycemia<br>Past medical history<br>Functional inquiry<br>Family history<br>Risk factors<br>Medications<br>Sexual function<br>Lifestyle | DM-directed history<br>Screen for awareness and frequency of hypoglycemia and DKA<br>Glucose monitoring<br>Use of insulin and oral agents<br>Smoking cessation | DM-directed history<br>Screen for awareness and frequency of hypoglycemia and DKA<br>Glucose monitoring<br>Use of insulin and oral agents<br>Sexual function<br>Lifestyle counselling<br>Screen for depression |
| **Physical Exam** | General: height, weight, BMI, BP, WC<br>Head and neck: fundoscopy, thyroid exam<br>Cardiovascular exam: signs of PVD, pulses, bruits<br>Abdominal exam (e.g. for organomegaly)<br>Hand/foot/skin exam<br>Neurological exam | Wt, BP, BMI, WC | Foot exam for sensation (using a 10 g monofilament), ulcers or infection<br>Remainder of exam as per PHE |
| **Investigations** | FBG, HbA1c, fasting lipids, Cr, microalbumin:creatinine ratio<br>Baseline ECG; repeat testing q2yr for those at high risk | HbA1c q3mo<br>FBG as needed | Fasting lipid profile<br>Annual random ACR and eGFR |
| **Management** | Nutritional and physical education<br>Consider referral to DM education program if available<br>Monitoring blood glucose: explain methods and frequency<br>Medication counselling: oral hypoglycemics and/or insulin, method of administration, dosage adjustments<br>Pneumococcal vaccination<br>Ophthalmology consult<br>type 1 DM within 5 yr<br>type 2 DM at diagnosis | Assess progress towards long-term complications<br>Adjust treatment plan if necessary | Calibrate home glucose monitor<br>Arrange retinopathy screening<br>Influenza vaccination annually |

**Calculate Total Insulin Required**
type 1 DM: 0.5-0.7 units/kg/d
type 2 DM: 0.3 units/kg/d

**Dietary Advice for Treatment of Type 2 DM in Adults**
Cochrane DB Syst Rev 2007;3:CD004097
**Purpose**: To assess the effects of type and frequency of different dietary advice strategies for adults with type 2 diabetes.
**Methods**: Systematic review of RCTs with follow-up of 6 mo or longer, where dietary advice was the main intervention.
**Results**: 36 RCTs with 1467 participants were included, all measuring weight and glycemic control measures, and some reporting mortality, blood pressure, serum cholesterol and triglycerides, maximal exercise capacity and compliance. No data was available for efficacy of dietary advice in terms of dietary changes. Adoption of regular exercise was found to promote HbA1c glycemic control in type 2 diabetic patients.
**Conclusion**: No high-quality data is available for the efficacy of dietary treatment of type 2 diabetes, though exercise has been shown to improve HbA1C at 6 and 12 mo follow-up in patients.

## Nonpharmacologic Management

- diet
  - can reduce HbA1c by 1-2%
  - moderate weight loss (5%) improves glycemic control and CVD risk factors
  - all diabetics should see a registered dietician for nutrition counselling
  - decrease combined saturated fats and trans-fatty acids to <10% of calories
  - avoid simple sugars, choose low glycemic-index foods, ensure regularity in timing and spacing of meals
- physical activity and exercise
  - at least 150 min of aerobic exercise plus 2 sessions of resistance training per wk is recommended
  - encourage 30-45 min of moderate exercise 4-7 d/wk
  - promote cardiovascular fitness: increases insulin sensitivity, lowers BP, and improves lipid profile
  - if using insulin, may require alterations of diet, insulin regimen, injection sites, and self-monitoring

## Self-Monitoring of Blood Glucose

- type 1 DM: 3 or more self-tests/d is associated with a 1% reduction in HbA1c
- type 2 DM: recommendations vary based on treatment regimen (e.g. insulin dependent requires more frequent monitoring – refer to 2013 Canadian Practice Guidelines)
- if FBG >14 mmol/L, perform ketone testing to rule out DKA
- if bedtime level is <7 mmol/L, have bedtime snack to reduce risk of nocturnal hypoglycemia

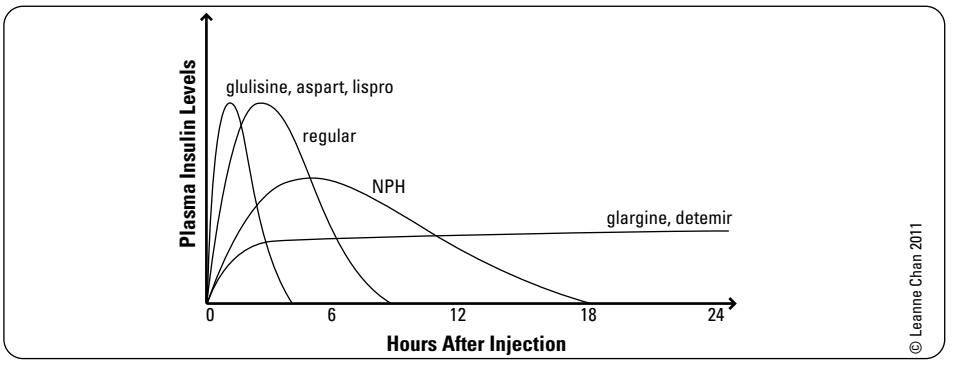



**Figure 9. Types of insulin preparation**

**At diagnosis of Type 2 DM**
Start lifestyle intervention (nutrition therapy and physical activity) ± Metformin

| A1C <8.5% | A1C ≥8.5% | Symptomatic hyperglycemia with metabolic decompensation |
|---|---|---|
| If not at glycemic target (2-3 mo) | Start **metformin immediately** Consider initial combination with another antihyperglycemic agent | Initiate **insulin ± metformin** |
| Start or increase **metformin** → | If not at glycemic targets | |

**Add another agent best suited to the individual by prioritizing patient characteristics:**

| PATIENT CHARACTERISTIC | CHOICE OF AGENT |
|---|---|
| **Priority:** Clinical cardiovascular disease | → SGLT2 inhibitor with demostrated CV outcome benefit |
| • Degree of hyperglycemia<br>• Risk of hypoglycemia<br>• Overweight or obesity<br>• Cardiovascular disease<br>• Comorbidities (renal, CHF, hepatic)<br>• Preferences and access to treatment | • Consider relative A1C lowering<br>• Rare hypoglycemia<br>• Weight loss or weight neutral<br>• Effect on cardiovascular outcome<br>• See therapeutic considerations, consider eGFR<br>• See cost column; consider access |

**Add another class of agent best suited to the individual** (classes listed in alphabetical order):

| Class | Relative A1C Lowering | Hypoglycemia | Weight | Effect in Cardiovascular Outcome Trial | Other Therapeutic Considerations | Cost |
|---|---|---|---|---|---|---|
| α-Glucosidase inhibitor (acarbose) | ↓ | Rare | Neutral to↓ | | Improved postprandial control, GI side-effects | $$ |
| Incretin agents: DPP-4 inhibitors | ↓↓ | Rare | Neutral to↓ | Neutral (alo, saxa, sita) | Caution with saxagliptin in heart failure | $$$ |
| GLP-1R agonists | ↓↓ to ↓↓↓ | Rare | ↓↓ | Neutral (lixi) | GI side effects | $$$$ |
| Insulin | ↓↓↓ | Yes | ↑↑ | Neutral (glar) | No dose ceiling, flexible regiments | $-$$$$ |
| Insulin secretagogue; Meglitinide | ↓↓ | Yes | ↑ | | Less hypoglycemia in context of missed meals, but usually requires TID to QID dosing | $$ |
| Sulfonylurea | ↓↓ | Yes | ↑ | | Gliclazide and glimepiride associated with less hypoglycemia than glyburide | $ |
| SGLT2 inhibitors | ↓↓ to ↓↓↓ | Rare | ↓↓ | Superior (empa in T2DM patients with clinical CVD) | Genital infections, UTI, hypotension, dose-related changes in LDL-C, caution with renal dysfunction and loop diuretics, dapagliflozin not to be used if bladder cancer, rare diabetic ketoacidosis (may occur with no hyperglycemia) | $$$ |
| Thiazolidinediones | ↓↓ | Rare | ↑↑ | Neutral | CHF, edema, fractures, rare bladder cancer (ploglitazone), cardiovascular controversy (rosiglitazone), 6-12 wk required for max effect | $$ |
| Weight loss agent (orlistat) | ↓ | None | ↓ | | GI side-effects | $$$ |

A1C = glycated hemoglobin; alo = alogliptin; CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase 4; empa = empagliflozin; GI = gastrointestinal; glar = glargine; GLP-1 = glucagon-like peptide 1; lixi = lixisenatide; saxa = saxagliptin; sita = sitagliptin; TZD = thiazolidinedione

**If not at glycemic targets**

Add another agent from a different class; add or intensify insulin regimen

**Make timely adjustments to attain target A1C within 3-6 mo**

**Note:** Physicians should refer to the most recent edition of the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and for detailed prescribing information

**Figure 10. Management of hyperglycemia in type 2 diabetes**
With permission of: Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Pharmacologic Management of Type 2 Diabetes. Can J Diabetes 2013;37:S61-S68

### Hypoglycemic Agents (Type 2 DM)

- oral
  - biguanide: metformin (Glucophage®)
  - thiazolidinedione: troglitazone (Rezulin®), rosiglitazone (Avandia®)
  - α-glucosidase inhibitor: acarbose (Precose®)
  - nonsulfonylureas: nateglinide (Starlix®), repaglinide (Gluconorm®)
  - sulfonylureas: glyburide (DiaBeta®), glimepiride (Amaryl®), gliclazide (Diamicron®)
  - DPP-4 inhibitor: sitagliptin (Januvia®)
- injectable
  - GLP-1 analogue: liraglutide (Victoza®)

### Other Medications Used in DM

- ACEI or ARB in those with any of:
  - clinical macrovascular disease
  - age ≥55
  - age <55 and microvascular complications
- statin in those with any of:
  - clinical macrovascular disease
  - age ≥40
  - age <40 and any of the following:
    - diabetes duration >15 yr and age >30 yr
    - microvascular complications
    - other cardiovascular risk factors
- low dose ASA (81-325 mg)
  - for secondary prevention in people with established CVD (NOT to be used routinely for primary prevention)

**Rosiglitazone Revisited: An Updated VertiMeta-Analysis of Risk for Myocardial Infarction and Cardiovascular Mortality**
Arch Intern Med 2010;170:1191-1201
**Purpose**: To evaluate the effectiveness of rosiglitazone on myocardial infarctions (MIs) and mortality.
**Methods**: Systematic review of RCTs of rosiglitazone, lasting at least 24 wk in duration, and reporting cardiovascular (CV) adverse events. Main outcomes were MIs, CV-related mortality and all-cause mortality.
**Results**: Rosiglitazone significantly increased MI risk (odds ratio (OR) 1.28, 95% CI 1.02-1.63, p=0.04) but not CV mortality (OR 1.03, 0.78-1.36, p=0.86).
**Conclusion**: Rosiglitazone continues to demonstrate increased risk of MIs, though it is not associated with increased risk of CV or all-cause mortality.

# Dizziness

- see Otolaryngology, OT6

### Epidemiology

- 70% of affected patients see general practitioners initially; 4% are referred to specialists
- frequency is proportional to age; commonest complaint of ambulatory patients age >75

### Differential Diagnosis

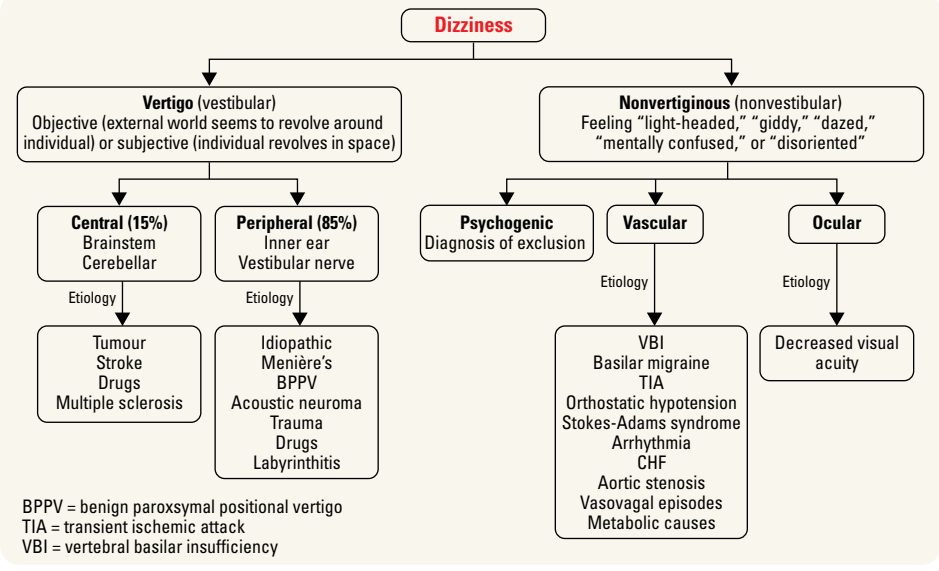



**Figure 11. Differential diagnosis of dizziness**

**Differential Diagnosis of Vertigo**

| | BPPV | Labyrinthitis | Menière's | Acoustic Neuroma |
|---|---|---|---|---|
| Onset | sudden | sudden | gradual | insidious |
| Duration | seconds | days | min-h | chronic |
| Hearing Loss | — | + | + | + |
| Tinnitus | — | + | + | + |
| Neuro Sx | — | — | — | + |

### History

- clarify type of dizziness: vertigo, pre-syncope, disequilibrium, light-headedness
- duration
- exacerbations
  - worse with head movement or eye closure (vestibular)
  - no change with head movement and eye closure (nonvestibular)
  - worse with exercise (cardiac/pulmonary causes)
- associated symptoms
  - neurologic (central)
    - transient diplopia, dysphagia, dysarthria, ataxia (TIA, VBI, migraine)
    - persistent headache, alterations in level of consciousness, sensory and/or motor deficits (CNS)

  - audiologic (peripheral)
    - hearing loss, tinnitus, otalgia, aural fullness
  - others
    - N/V (peripheral vestibular disorders)
    - SOB, palpitations (hyperventilation, cardiac problem)
- general medical history
  - HTN, DM, heart disease, fainting spells, seizures, cerebrovascular disease, migraines
  - ototoxic drugs: aminoglycosides (gentamicin, streptomycin, tobramycin), erythromycin, ASA, antimalarials
  - hypotension (secondary to diuresis): furosemide, caffeine, alcohol
  - depression/anxiety: can present with light-headedness

### Physical Exam/Investigations
- syncopal
  - cardiac (orthostatic changes in vitals), peripheral vascular, and neurologic exams
  - blood work, ECG, 24 h Holter, treadmill stress test, loop ECG, tilt table testing, carotid, vertebral doppler, and EEG
- vertiginous
  - ENT and neurologic exams
  - Dix-Hallpike, consider audiometry and MRI if indicated
- non-syncopal, non-vertiginous
  - assess gait, vision and test for neuropathy
  - cardiac and neurologic exams (cerebellar and cranial nerve function)
  - 3 min hyperventilation trial (patient is coached to hyperventilate until patient becomes dizzy to identify if symptoms are reproducible and confirm that hyperventilation is the etiology of the symptoms), ECG, EEG
  - Romberg test: test for disequilibrium (patient sways towards the side of vestibular dysfunction)



**Dix-Hallpike Test**
- Have the patient seated with legs extended and head at 45° rotation
- Rapidly shift patient to supine position with head fully supported in slight extension (for 45 s)
- Observe for rotatory nystagmus and ask about sensation of vertigo

### Treatment
- guided by history, physical exam, and investigations
- include education, lifestyle modification, physical maneuvers (e.g. Epley for BPPV), symptomatic management (e.g. antiemetics), pharmacotherapy, and surgery
- refer when significant central disease is suspected, when vertigo of peripheral origin is persistent (lasting >2-4 wk), or if atypical presentation

# Domestic Violence/Elder Abuse

## INTIMATE PARTNER VIOLENCE

### Definition
- includes physical, sexual, emotional, psychological, and financial abuse

### Epidemiology
- lifetime prevalence of intimate partner violence against women is between 25-30%
- similar prevalence of intimate partner violence against men, who may be less likely to report due to social stigma
- women who experience abuse have increased rates of injury, death, and health consequences including 50-70% increase in gynecological, central nervous system, and stress-related problems
- occurs in all socioeconomic, educational, and cultural groups with increased incidence in pregnancy, disabled women, bisexuality, and 18-24 age group
- 25-50% chance of child abuse or neglect in families where partner abuse occurs; children exposed to violence in the home are more likely to experience or perpetrate violence later in life (Cycle of Violence)
- physician recognition rates as low as 5%

### Presentation
- multiple visits with vague, ill-defined complaints such as: headaches, gastrointestinal symptoms, insomnia, chronic pain, hyperventilation
- may also present with injuries inconsistent with history

### Management
- screen ALL patients
  - always have a high index of suspicion
  - asking about abuse is the strongest predictor of disclosure
  - several screening tools (see sidebar) exist to identify victims of partner violence
  - make sure to determine the victim's level of immediate and long-term danger and ask if there are weapons in the house
- ensure patient safety
  - victim most at risk for homicide when attempting to leave home or following separation
  - safety planning includes ensuring that there is access to an exit in the home, establishing a safe place to go, and having emergency items prepared should the patient need to leave quickly (including money, clothes, keys, medications, and important documents)



**Screening Instruments for Domestic Violence**

**A) Woman Abuse Screening Tool (WAST)-SHORT**

1. In general how would you describe your relationship?
   a. A lot of tension
   b. Some tension
   c. No tension
2. Do you and your partner work out arguments with . . .?
   a. Great difficulty
   b. Some difficulty
   c. No difficulty

Endorsing either question 1 ("a lot of tension") or question 2 ("great difficulty") makes intimate partner violence exposure likely

**B) HITS**

How often does your partner:
1. Physically hurt you?
2. Insult you?
3. Threaten you with harm?
4. Scream or curse at you?

Each question on HITS to be answered on a 5 point scale ranging from 1 (= never) to 5 (= frequently)
A total score of 10 or greater is significant

- provide community resources
  - shelter or helpline number with legal advocacy and counselling services
  - involve social workers or domestic violence advocates
- appointment for follow-up to assess whether condition is better or worse
- reassure patient that she/he is not to blame and that the assault is a crime
  - goal is to convey the message that "As your doctor, I am concerned for your safety" and "Your partner has a problem that he/she needs help with" and "I want to help you"
  - reporting suspected or known child abuse is mandatory
  - spousal abuse is a criminal act, but not reportable without the woman's/man's permission
- DOCUMENT all evidence of abuse-related visits for medico-legal purposes

### ELDER ABUSE
- see Geriatric Medicine, GM10

# Dyspepsia

- see Gastroenterology, G10

### Definition and Clinical Features
- defined as epigastric pain or discomfort
- can be associated with fullness, belching, bloating, heartburn, food intolerance, N/V

### Epidemiology
- annual incidence 1-2%, prevalence 20-40%

### Etiology
- common: functional, PUD, GERD, gastritis
- others: cholelithiasis, irritable bowel syndrome, esophageal or gastric cancer, pancreatitis, pancreatic cancer, Zollinger-Ellison syndrome, and abdominal angina

### History
- symptoms may not be useful in finding cause
- associated with eating, anorexia, N/V, alcohol, NSAID use
- red flags: vomiting, bleeding/anemia, abdominal mass, dysphagia (VBAD)

### Investigations and Management
- for new onset dyspepsia:
- <60 yr without high risk features, test for *H. pylori* using the urea breath test or serology
- ≥60 yr should undergo upper endoscopy to rule out organic pathology
- lifestyle modifications: decrease caffeine and alcohol intake, avoid citrus food, smaller and more frequent meals, avoid supine position right after meals, smoking cessation
- pharmacologic treatment
  - gastric acid suppression: H2 blockers, PPIs; both are effective for PUD and GERD
  - TCAs or prokinetics: e.g. Metoclopramide; effective for functional dyspepsia
- *H. pylori* eradication
- do not keep patients on PPI without at least 1 trial off the medication per year (https://choosingwiselycanada.org/perspective/ppi-toolkit/)
- for non-responders, upper endoscopy should be considered; if endoscopy is negative, defined as functional dyspepsia

**Dyspepsia Red Flags**
- Weight Loss
- Dysphagia
- Persistent vomiting
- GI bleeding (hematemesis, hematochezia, melena)
- Onset age >50

***H. pylori* Eradication**
Take the following 10 d treatment
1) PPI 1 tablet 2x/d for 10 d and
2) Amoxicillin 1 g twice a day for 5 d (day 1-5)
Followed by
3) Clarithromycin 500 mg 2x/d (day 6-10) and
4) Metronidazole 500 mg 2x/d (day 6-10)

# Dyspnea

- see Respirology, R3 and Emergency Medicine, ER26

### Definition
- uncomfortable, abnormal awareness of breathing

### History and Physical Exam
- history
  - cough, sputum, hemoptysis, wheezing, chest pain, palpitations, dizziness, edema, SOB
  - constitutional symptoms
  - history of asthma, allergies, eczema, ASA/NSAID sensitivity, nasal polyps
  - smoking, recreational drugs, medications
  - occupational exposure, environmental exposure (e.g. pets, allergens, smoke)
  - travel and birth place
  - FHx of atopy
  - previous CXR or PFTs
- physical exam: vitals, respiratory, precordial, HEENT, signs of anemia/liver failure/heart failure

**Differential Diagnosis of Dyspnea**

**Pulmonary**
- COPD
- Asthma
- Restrictive lung disease
- Pneumothorax
- Congenital lung disease
- PE

**Cardiac**
- CHF
- CAD
- MI (recent or past)
- Cardiomyopathy
- Valve dysfunction
- Pericarditis
- Arrhythmia
- Hypertrophy

**Mixed/Other**
- Deconditioning
- Trauma
- Pain
- Neuromuscular
- Metabolic condition
- Functional: anxiety, panic attack, hyperventilation

### Investigations
- CXR, ECG
- PFTs, ABG acutely if indicated

### Management
- ABCs: send to ED if in severe respiratory distress
- depends on cause

# Dysuria

- see Urology, U10

### Definition
- the sensation of pain, burning, or discomfort on urination

### Epidemiology
- in adulthood, more common in women than men
- approximately 25% of women report one episode of acute dysuria per yr
- most common in women age 25-54 and in those who are sexually active
- in men, dysuria becomes more prevalent with increasing age

### Etiology
- infectious
  - most common cause
  - presents as cystitis, urethritis, pyelonephritis, vaginitis, cervicitis, epididymo-orchitis, or prostatitis
- non-infectious
  - hormonal conditions (hypoestrogenism), obstruction (BPH, urethral strictures), allergic reactions, radiation, drugs/chemicals, foreign bodies, trauma, neoplasm, kidney stones, inflammatory diseases, endometriosis, psychogenic

**Table 13. Etiology, Signs and Symptoms of Common Causes of Dysuria**

| Infection | Etiology | Signs and Symptoms |
|---|---|---|
| **UTI/Cystitis** | KEEPS bacteria (*Klebsiella, E. coli, Enterobacter, Proteus mirabilis, Pseudomonas, S. saprophyticus*) | Internal dysuria throughout micturition, frequency, urgency, incontinence, hematuria, nocturia, back pain, suprapubic discomfort, low grade fever (rare) |
| **Urethritis** | *C. trachomatis, N. gonorrhoeae, Trichomonas, Candida*, herpes | Initial dysuria, urethral/vaginal discharge, history of STI |
| **Vaginitis** | *Candida, Gardnerella, Trichomonas, C. trachomatis*, atrophic, herpes, lichen sclerosis | External dysuria/pain, vaginal discharge, irritation, dyspareunia, abnormal vaginal bleeding |
| **Prostatitis** | *E. coli, C. trachomatis, S. saprophyticus, Proteus mirabilis, Enterobacter, Klebsiella, Pseudomonas* | Dysuria, fever, chills, urgency, frequency, tender prostate, rectal pain |
| **Pyelonephritis** | *E. coli, S. saprophyticus, Proteus mirabilis, Enterobacter, Klebsiella, Pseudomonas* | Internal dysuria, fever, chills, flank pain radiating to groin, CVA tenderness, N/V |

### Investigations
- no investigations necessary when history and physical consistent with uncomplicated UTI – treat empirically (urinalysis can be performed when indicated by dipstick or microscopy)
- urinalysis/dipstick: positive for nitrites and leukocytes
- urine R&M: pyuria, bacteriuria, hematuria
- urine C&S
- CBC and differential if suspecting pyelonephritis
- if vaginal/urethral discharge present: wet mount, Gram stain, KOH test, vaginal pH, culture for yeast and trichomonas, endocervical/urethral swab or urine PCR for *N. gonorrhoeae* and *C. trachomatis*
- radiologic studies and other diagnostic tests if atypical presentation
- see Pediatrics, P60 for UTI

### Management
- UTI/cystitis
  - pregnant women with bacteriuria (2-7%) must be treated even if asymptomatic due to increased risk of pyelonephritis, preterm labour, low birth weight, and perinatal mortality; need to follow with monthly urine cultures and repeat if still infected
  - patients with recurrent UTIs (>3/yr) should be considered for prophylactic antibiotics
  - if complicated UTI, patients require longer courses of broader spectrum antibiotics
- urethritis
  - positive swab or PCR for chlamydia or gonorrhea must be reported to Public Health
  - all patients should return 4-7 d after completion of therapy for clinical evaluation



**UTI Clinical Decision Aid**
*Arch Intern Med* 2007;67:2201-2206
- Dysuria
- +Leukocytes
- +Nitrites

If 2 or more criteria met, then treat without culture, otherwise culture required prior to treatment



**Risk Factors for Complicated UTI**
- Male
- Pregnancy
- Recent urinary tract instrumentation
- Functional or anatomic abnormality of the urinary tract
- Chronic renal disease
- DM
- Immunosuppression
- Indwelling catheter



**Cranberries for Preventing Urinary Tract Infections**
Cochrane DB Syst Rev 2008;1:CD001321
**Study:** Meta-analysis of 10 RCTs (n=1049).
**Patients:** All populations.
**Intervention:** Cranberry juice vs. placebo, juice or water was evaluated in seven studies, and cranberry tablets vs. placebo in four studies.
**Main Outcome**: UTIs – symptomatic and asymptomatic.
**Results:** Cranberry products significantly reduced the incidence of UTIs at 12 mo (RR 0.65, 95% CI 0.46-0.90) compared with placebo/control.
**Conclusion:** There is some evidence that cranberry products may decrease the number of symptomatic UTIs over a 12 mo period, particularly for women with recurrent UTIs.



**Prevention of UTIs**
- Maintain good hydration (especially with cranberry juice) (recommendation level I)
- Wipe urethra from front to back to avoid contamination of the urethra with feces from the rectum
- Avoid feminine hygiene sprays and scented douches
- Empty bladder immediately before and after intercourse

# Epistaxis

- see Otolaryngology, OT26

# Erectile Dysfunction

- see Urology, U33

## Definition
- consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual performance of ≥3 mo duration

## Epidemiology
- ~20% of men age 40; ~50% of men age 70

## Etiology
- organic: vascular (90%) (arterial insufficiency, atherosclerosis), endocrine (low testosterone, DM), anatomic (structural abnormality, e.g. Peyronie's), neurologic (post-operative, DM), medications (clonidine, antihypertensives, psychotropics)
- psychogenic (10%)

**Table 14. Differentiation Between Organic and Psychogenic ED**

| Characteristic | Organic | Psychogenic |
|---|---|---|
| **Onset** | Gradual | Acute |
| **Circumstances** | Global | Situational |
| **Course** | Constant | Varying |
| **Non-Coital Erection** | Poor | Rigid |
| **Morning Erection** | Absent | Present |
| **Psychosexual Problem** | Secondary | Long history |
| **Partner Problem** | Secondary | At onset |
| **Anxiety and Fear** | Secondary | Primary |

Walsh PC, Campbell MF, Retik AB. Campbell's Urology, 8th ed. W.B. Saunders, 2002.Table 46-4

## History
- comprehensive sexual, medical, and psychosocial history
- time course
  - last satisfactory erection
  - gradual or sudden onset
  - attempts at sexual activity
- quantify
  - presence of morning or night time erections
  - stiffness (scale of 1-10)
  - ability to initiate and maintain an erection with sexual stimulation
  - erection stiffness during sex (scale of 1-10)
- qualify
  - partner or situation specific
  - loss of erection before penetration or climax
  - degree of concentration required to maintain an erection
  - percentage of sexual attempts satisfactory to patient and/or his partner
  - significant bends in penis or pain with erection
  - difficulty with specific positions
  - impact on quality of life and relationship

## Investigations
- hypothalamic-pituitary-gonadal axis evaluation: testosterone (free + total), prolactin, LH
- risk factor evaluation: fasting glucose, HbA1c, lipid profile
- others: TSH, CBC, urinalysis
- specialized testing
  - psychological and/or psychiatric consultation
  - in-depth psychosexual and relationship evaluation
  - nocturnal penile tumescence and rigidity (NPTR) assessment
  - vascular diagnostics (e.g. doppler studies, angiography)



**Differential Diagnosis of Erectile Dysfunction**

**PENIS**
**P**sychogenic
**E**ndocrine (type 2 DM, testosterone)
**N**eurogenic (type 2 DM, post-operative)
**I**nsufficiency of blood (atherosclerosis)
**S**ubstances



**The Effect of Lifestyle Modification and Cardiovascular Risk Factor Reduction on Erectile Dysfunction**
Arch Intern Med 2011;171:1797-1803
**Purpose**: To evaluate the effectiveness of lifestyle interventions and pharmacotherapy for cardiovascular (CV) risk factors on severity of erectile dysfunction (ED).
**Methods**: Meta-analysis of RCTs with a follow-up of a minimum of 6 wk, evaluating lifestyle intervention versus pharmacotherapy for CV risk factor reduction. Main outcome measure was weighted mean differences in the International Index of Erectile Dysfunction (IIEF-5) score.
**Results**: 6 RCTs with a total of 740 participants were included. Lifestyle modifications and pharmacotherapy for CV risk factor reduction were both associated with significant improvements in sexual function based on IIEF-5 scores (weighted mean difference (WMD) 2.66, 95% CI 1.86-3.47). Excluding statin trials, lifestyle modification interventions were associated with a statistically significant improvement in sexual function (WMD 2.40, 1.19-3.61).
**Conclusion**: Lifestyle modifications and pharmacotherapy for CV risk reduction are effective in improving male sexual function.



**Reasons for Referral to Urology**
- Significant penile anatomic disease
- Younger patient with a history of pelvic or perineal trauma
- Cases requiring vascular or neuro-surgical intervention
- Complicated endocrinopathies
- Complicated psychiatric or psychosocial problems
- Patient or physician desire for further evaluation

### Management

**Table 15. Management of Erectile Dysfunction**

| Nonpharmacologic | Pharmacologic | Surgical |
|---|---|---|
| Lifestyle changes (alcohol, smoking, exercise)<br>Relationship/sexual counselling<br>Vacuum devices | Oral agents<br>Suppository<br>Male urethral suppository for erection (MUSE)<br>Injections | Implants<br>Vascular repair<br>Realignment |

- pharmacologic treatment
  - phosphodiesterase type 5 inhibitors
  - α-adrenergic blockers (e.g. yohimbine)
  - serotonin antagonist and reuptake inhibitor (e.g. trazodone)
  - testosterone – currently only indicated in patients presenting with hypogonadism and testosterone deficiency (note: breast/prostate cancer are absolute contraindications)

**Table 16. Phosphodiesterase Type 5 Inhibitors**

| Examples | Dosing (1 dose/d) | Specifics | Side Effects | Contraindications |
|---|---|---|---|---|
| sildenafil (Viagra®) | 25-100 mg/dose | Take 0.5-4 h prior to intercourse<br>May last 24 h | Flushing, headache, indigestion | Not to be used in patients taking nitrates |
| tadalafil (Cialis®) | 5-20 mg/dose | Effects may last 36 h | As above | As above |
| vardenafil (Levitra®) | 2.5-20 mg/dose | Take 1 h prior to intercourse | As above | As above |

# Fatigue

### Definition
- can describe difficulty or inability to initiate activity, maintain activity, or difficulty with concentration/memory
- try to determine what the patient means e.g. excessive sleepiness, muscle weakness, decreased exercise tolerance, mood concerns

**Fatigue Red Flags**
- Fever
- Weight loss
- Night sweats
- Neurological deficits
- Ill-appearing

### Epidemiology
- 25% of office visits to family physicians
  - peaks in ages 20-40
  - F:M = 3-4:1
- 50% have associated psychological complaints/problems, especially if <6 mo duration

### Differential Diagnosis

**Table 17. Differential Diagnosis of Fatigue: PS VINDICATE**

| | | |
|---|---|---|
| **P** | **Psychogenic** | **Depression, life stresses**, anxiety disorder, chronic fatigue syndrome, fibromyalgia |
| | Physiologic | **Pregnancy, caregiving demands (young children, elderly)** |
| **S** | Sleep disturbance | **Obstructive sleep apnea, sleep disorder,** poor sleep hygiene, BPH, shift work, pain |
| | Sedentary | Unhealthy/sedentary lifestyle |
| **V** | Vascular | Stroke |
| **I** | **Infectious** | Viral (e.g. mononucleosis, hepatitis, HIV), bacterial (e.g. TB), fungal, parasitic |
| **N** | **Neoplastic** | Any malignancy |
| | Nutrition | **Anemia** ($Fe^{2+}$ deficiency, $B_{12}$ deficiency) |
| | Neurogenic | Myasthenia gravis, multiple sclerosis, Parkinson's disease |
| **D** | **Drugs** | β-blockers, antihistamines, anticholinergics, benzodiazepines, antiepileptics, antidepressants |
| **I** | Idiopathic | |
| **C** | Chronic illnesses | CHF, lung diseases (e.g. COPD, sarcoidosis), renal failure, chronic liver disease |
| **A** | Autoimmune | SLE, RA, mixed connective tissue disease, polymyalgia rheumatica |
| **T** | Toxin | **Substance abuse** (e.g. alcohol), heavy metal |
| **E** | Endocrine | **Hypothyroidism, DM**, Cushing's syndrome, adrenal insufficiency, pregnancy |

Common causes are in **bold**

### Investigations
- psychosocial causes are common, so usually minimal investigation is warranted
- physical causes of fatigue usually have associated symptoms/signs that can be elicited from a focused history and physical exam
- investigations are guided by history and physical exam and may include:
  - CBC and differential, electrolytes, BUN, Cr, ESR, glucose, TSH, ferritin, vitamin $B_{12}$, serum protein electrophoresis, Bence-Jones protein, albumin, AST, ALT, ALP, bilirubin, calcium, phosphate, ANA, β-hCG
  - urinalysis, CXR, ECG
  - additional tests: serologies (Lyme disease, hepatitis B and C screen, HIV, ANA) and Mantoux skin tests

### Treatment
- treat underlying cause
- if etiology cannot be identified (1/3 of patients)
  - reassurance and follow-up, especially with fatigue of psychogenic etiology
  - supportive counselling, behavioural, or group therapy
  - encourage patient to stay physically active to maximize function
  - review all medications, OTC, and herbal remedies for drug-drug interactions and side effects
  - prognosis: after 1 yr, 40% are no longer fatigued

## CHRONIC FATIGUE SYNDROME

### Definition (CDC 2006) – must meet both criteria
1. new or definite onset of unexplained, clinically evaluated, persistent or relapsing chronic fatigue, not relieved by rest, which results in occupational, educational, social, or personal dysfunction
2. concurrent presence of ≥4 of the following symptoms for a minimum of 6 mo
   - impairment of short-term memory or concentration, severe enough to cause significant decline in function
   - sore throat
   - tender cervical or axillary lymph nodes
   - muscle pain
   - multi-joint pain with no swelling or redness
   - new headache
   - unrefreshing sleep
   - post-exertion malaise lasting >24 h
- exclusion criteria: medical conditions that may explain the fatigue, certain psychiatric disorders (depression with psychotic or melancholic features, schizophrenia, eating disorders), substance abuse, severe obesity (BMI >45)

### Epidemiology
- F>M, Caucasians > other groups, majority in their 30s
- found in <5% of patients presenting with fatigue

### Etiology
- unknown, likely multifactorial
- may include infectious agents, immunological factors, neurohormonal factors, and/or nutritional deficiency

### Investigations
- no specific diagnostic laboratory tests

### Treatment
- promote sleep hygiene
- provide support and reassurance that most patients improve over time
- non-pharmacological
  - regular physical activity, optimal diet, psychotherapy (e.g. CBT), family therapy, support groups
- pharmacological
  - to relieve symptoms: e.g. antidepressants, anxiolytics, NSAIDs, antimicrobials, antiallergy therapy, antihypotensive therapy

**Exercise Therapy for Chronic Fatigue**
Cochrane DB Syst Rev 2017;4:CD003200
**Purpose**: To determine the effectiveness of exercise therapy for chronic fatigue syndrome (CFS).
**Methods**: Meta-analysis of RCTs involving adults with CFS as a primary diagnosis who were able to participate in exercise therapy. Studies compared exercise therapy to passive control, psychological therapies, adaptive pacing therapy or pharmacological therapy.
**Results**: 8 RCTs with 1518 participants were included. Exercise therapy lasted 12 to 26 wk in duration. Moderate-quality evidence showed exercise therapy was more effective in reducing fatigue relative to passive or no treatment, and was also associated with a positive effect on daily physical functioning, sleep and self-rated overall health. One study suggested exercise therapy was more effective than pacing strategies for fatigue reduction, though was no more effective than cognitive behavioural therapy (CBT). Exercise therapy was not found to worsen symptoms for CFS patients, and serious side-effects were rare across all intervention groups.
**Conclusion**: Exercise therapy may be beneficial to overall health and may decrease fatigue in CFS patients, and is not associated with worsening outcomes. Therapy may also have a positive impact on sleep, physical function, and self-perceived general health. In general, exercise therapy appears more effective than pacing strategies, and similar to CBT.

# Fever

- see Pediatrics, P49

### Definition
- oral temperature >37.2°C (AM), 37.7°C (PM)
- fever in children under 2 must be a rectal temperature for accuracy
- TM not accurate for measurement until child is >5 yr

**Table 18. Differential Diagnosis of Fever**

| Infection | Cancer | Medications | | Other |
|---|---|---|---|---|
| Bacterial | Leukemia | Allopurinol | Nifidepine | Irritable Bowel Syndrome |
| Viral | Lymphoma | Captopril | Phenytoin | Collagen Vascular Disease |
| TB | Other Malignancies | Cimetidine | Diuretics | DVT |
| | | Heparin | Barbiturates | |
| | | INH | Antihistamines | |
| | | Meperidine | | |

### History
- fever
  - peak temperature, thermometer, route, duration
  - time of day
  - response to antipyretics
- systemic symptoms
  - weight loss, fatigue, rash, arthralgia, night sweats
- symptoms of possible source
  - UTI/pyelonephritis: dysuria, foul-smelling urine, incontinence, frequency, hematuria, flank pain
  - pneumonia: cough, pleuritic chest pain
  - URTI: cough, coryza, ear pain
  - meningitis: headache, confusion, stiff neck, rash
  - osteomyelitis: bone pain
  - skin: purulent discharge
  - PID: discharge, dyspareunia, lower abdominal pain
  - gastroenteritis: abdominal pain, diarrhea, blood per rectum, vomit
  - medications
  - PE/DVT: swollen legs, pain in calf, SOB, pleuritic chest pain
  - history of cancer/family history of cancer
- infectious contacts
  - travel history, camping, daycare, contact with TB, foodborne, animals

### Possible Investigations
- CBC and differential, blood culture, urine culture, urinalysis
- stool O&P, Gram stain, culture
- CXR, Mantoux skin test, sputum culture
- lumbar puncture

### Management
- increase fluid intake
- general: sponge bath, light clothing
- acetaminophen/ibuprofen as needed
- treat underlying cause

## Headache

### Primary Headaches
- see Neurology, N44

### Secondary Headaches
- caused by underlying organic disease
- account for <10% of all headaches, may be life-threatening

### Etiology
- drug: drug withdrawal, medication overuse, drug side effect, and carbon monoxide
- infectious: meningitis, encephalitis, abscess
- vascular: aneurysm, stroke, subarachnoid hemorrhage, hypertension, and temporal arteritis
- endocrine: thyroid disease, pheochromocytoma
- neoplastic: tumour
- trauma: TMJ injury, c-spine injury, head injury, subdural hematoma, and subarachnoid hemorrhage
- other: serious ophthalmological and otolaryngological causes

### Investigations
- indicated only when red flags are present and may include:
  - CBC for suspected systemic or intracranial infection
  - ESR for suspected temporal arteritis
  - neuroimaging (CT or MRI) to rule out intracranial pathology
  - CSF analysis for suspected intracranial hemorrhage, infection

### Management
- based on underlying disorder
- analgesics may provide symptomatic relief



**Acupuncture for Migraine Prophylaxis**
Cochrane DB Syst Rev 2016:6:CD001218
**Purpose**: To investigate whether acupuncture is more effective than no prophylactic treatment, routine care only or sham acupuncture, and whether it is as effective as prophylactic pharmacological treatment, in terms of reducing headache frequency in adults with episodic migraine.
**Methods**: Meta-analysis of RCTs with a minimum of an 8 wk duration, comparing acupuncture intervention with a no-acupuncture control (no prophylaxis, routine care, sham, or pharmacological prophylaxis).
**Results**: 22 trials with 4985 participants were included. Acupuncture was associated with moderate headache frequency reduction compared to no acupuncture (standardized mean difference (SMD) -0.56, 95% CI -0.65 to -0.48), and a reduction of >50% in headache frequency for 41% and 17% of participants receiving acupuncture and no acupuncture, respectively (pooled risk ratio (RR) 2.40, 2.08 to 2.76; number needed to treat (NNT) 4, 3 to 6). Acupuncture showed a small but statistically significant reduction over sham both post-treatment (SMD -0.18, -0.28 to -0.08) and post-follow-up (SMD -0.19, -0.30 to -0.09), with 50%+ headache frequency reduction being achieved in 50% versus 41% of those receiving acupuncture and sham, respectively (pooled RR 1.23, 1.11 to 1.36; NNT 11, 7 to 20); these numbers were 53% and 42%, respectively, post-follow-up (pooled RR 1.25, 1.13 to 1.39; NNT 10, 6 to 18). Number of participants dropping out and reporting adverse effects did not differ significantly between acupuncture and sham groups. Compared to pharmacological prophylaxis, a significant reduction in migraine frequency was noted with drugs (SMD -0.25, -0.39 to -0.10), but the significance was not maintained at follow-up. After 6 mo, headache frequency was halved in 59% of patients receiving acupuncture and 54% receiving prophylactic drugs (pooled RR 1.11, 0.97 to 1.26). Those receiving acupuncture were less likely to drop out due to adverse effects or to report adverse events than those receiving drugs.
**Conclusion**: Adding acupuncture to symptomatic treatment of attacks reduces frequency of headaches. Acupuncture is more effective than sham, and is similarly effective to pharmacological interventions for migraine prophylaxis.



**Migraine Screen**

**POUND**
**P**ulsatile quality
**O**ver 4-72 h
**U**nilateral
**N**ausea and vomiting
**D**isabling intensity
if ≥4 present then a diagnosis is likely (+LR = 24)



**Headache Red Flags**

**SNOOP**
**S**ystemic symptoms of illness
- fever
- anticoagulation
- pregnancy
- cancer

**N**eurologic signs/symptoms
- impaired mental status
- neck stiffness
- seizures
- focal neurological deficits

**O**nset
- sudden and severe
- new headache after age 50

**O**ther associated conditions
- following head trauma
- awakens patient from sleep
- jaw claudication
- scalp tenderness
- worse with exercise, sexual activity or Valsalva

**P**rior headache history
- different pattern
- rapidly progressing in severity/frequency

# Hearing Impairment

- see Otolaryngology, OT7

### Definition
- hearing impairment: a raised hearing threshold measured as decibels of hearing loss relative to the normal population at specific frequencies
- hearing disability: hearing impairment that interferes with performing daily tasks

### Epidemiology
- prevalence increases with age (6% of 35-44 yr old, 43% of 65-84 yr old)
- 90% of age-related hearing loss (presbycusis) is sensorineural
- hearing loss detectable by audiology is present in greater than 1/3 of people >65 yr

### Classification
- conductive (external sound does not reach the middle ear)
- sensorineural involving the inner ear, cochlea, or auditory nerve
- mixed

### Assessment
- infants: universal newborn hearing screening program
- elderly
  - whispered-voice test
    - examiner stand 0.6 metres behind the patient, whispers a combination of 6 letters/numbers, and asks the patient to repeat the sequence; test 1 ear at a time while masking the non-test ear simultaneously
  - tuning fork test (to distinguish conductive from sensorineural hearing loss)
    - Rinne and Weber (not for general screening)
  - formal audiologic assessment
- pure tone, air, and bone conduction testing
- speech audiometry
- impedance audiometry

### Management
- counsel about noise control and hearing protection programs (Grade A evidence)
- perform investigations in patients with unexplained sensorineural hearing loss
  - blood sugar, CBC and differential, TSH, syphilis testing
  - consider a CT/MRI for patients with progressive asymmetric sensorineural hearing loss to exclude vestibular schwannoma (acoustic neuroma)
- refer patients who
  - exhibit hearing loss for a complete audiological examination
  - have an unknown etiology to an ENT specialist
  - experience sudden sensorineural hearing loss to an ENT specialist (urgent, requires oral steroid Tx)
- treatment: hearing amplification (e.g. hearing aids), assistive listening devices, and cochlear implants can dramatically improve quality of life

**Does This Patient Have Hearing Impairment?**
JAMA 2006;295:416-428
**Purpose**: To evaluate bedside clinical maneuvers used to evaluate the presence of hearing impairment.
**Methods**: Systematic review of original studies examining the accuracy or precision of screening questions and tests.
**Results**: 24 studies were included.
**Conclusions**: Elderly patients acknowledging a hearing impairment require audiometry, while those who indicate they do not have hearing impairment should be screened with a whispered-voice test. A normal whispered-voice test requires no further workup, and those unable to perceive the whisper require audiometry. Weber and Rinne tests are not suitable for general hearing impairment screening.

# Hypertension

Hypertension Guidelines are reviewed and updated annually, for up-to-date recommendations, please see http://guidelines.hypertension.ca/

### Epidemiology
- 22% of Canadian adults suffer from HTN (prevalence is 52% in the 60-70 age group)
- lifetime risk of developing hypertension is approximately 90%
- 64% of Canadians who have HTN are treated and controlled, while 17% are unaware that they have HTN
- 3rd leading risk factor associated with death
  - risk factor for CAD, CHF, cerebrovascular disease, renal failure, peripheral vascular disease

### Definitions
- HTN
  - BP ≥140/90 mmHg (OBPM) ≥135/85 (ABPM/AOBP)
- isolated systolic HTN
  - sBP ≥140 and dBP <90
  - associated with progressive reduction in vascular compliance
  - usually begins in 5th decade
- hypertensive urgency
  - sBP >210 or dBP >120 with minimal or no target-organ damage

Symptoms of HTN are usually NOT PRESENT (this is why it is called the "silent killer").
May have occipital headache upon awakening or organ-specific complaints if advanced disease

**Renovascular HTN Suspected if Patient Presenting with 2 or more of:**
- Sudden onset or worsening of HTN and age >55 or <30 yr
- Presence of abdominal bruit
- HTN resistant to 3 or more drugs
- Rise in Cr of 30% or more associated with use of an ACEI or ARB
- Other atherosclerotic vascular disease, particularly in patients who smoke or have dyslipidemia
- Recurrent pulmonary edema associated with hypertensive surges

- hypertensive emergency
  - severe HTN (dBP >120) + acute target-organ damage
  - accelerated HTN
    - significant recent increase in BP over previous hypertensive levels associated with evidence of vascular damage on fundoscopy, but without papilledema
  - malignant HTN
    - sufficient elevation in BP to cause papilledema and other manifestations of vascular damage (retinal hemorrhages, bulging discs, mental status changes, increasing creatinine)
- white coat HTN
  - high clinic BP with normal home BP and 24 h ambulatory BP, caused by anxiety in clinic
- masked HTN
  - normal clinic BP with high BP in home and/or ambulatory setting, often provoked by anxiety, job stress, exercise

## Etiology
- essential hypertension (90%, undetermined cause)
- secondary hypertension (10%, known cause)

## Predisposing Factors
- family history
- obesity (especially abdominal)
- alcohol consumption
- stress
- sedentary lifestyle
- smoking
- male
- age >30
- excessive salt intake/fatty diet
- African American ancestry
- dyslipidemia

**Table 19. Causes of Secondary HTN**

| | Common Cause | | |
|---|---|---|---|
| **Renal** | Renovascular HTN<br>Renal parenchymal disease, glomerulonephritis, pyelonephritis, polycystic kidney | | |
| **Endocrine** | 1° hyperaldosteronism<br>Pheochromocytoma<br>Cushing's syndrome<br>Hyperthyroidism/hyperparathyroidism<br>Hypercalcemia of any cause | | |
| **Vascular** | Coarctation of the aorta<br>Renal artery stenosis | | |
| **Drug-Induced** | Estrogens/OCP<br>MAOIs<br>Cocaine | Steroids<br>Lithium<br>Amphetamines | NSAIDs<br>Decongestants<br>Alcohol |

## Investigations
- for all patients with HTN:
  - electrolytes, Cr, fasting glucose and/or HbA1c, lipid profile, 12-lead ECG, urinalysis
  - self-measurement of BP at home is encouraged (recommended devices listed at www.hypertension.ca)
- for specific patient etiology:
  - DM or chronic kidney disease: urinary protein excretion
  - if suspected renovascular HTN: renal ultrasound, captopril renal scan (if GFR >60 mL/min), MRA/CTA (if normal renal function)
  - if suspected endocrine cause: plasma aldosterone, plasma renin (aldosterone-to-renin ratio)
- measured from morning samples taken from patients in sitting position after resting 15 min
- discontinue aldosterone antagonists, ARBs, β-blockers, and clonidine prior to testing
  - if suspected pheochromocytoma: 24 h urine for metanephrines and creatinine
- if suspected LV dysfunction: echocardiogram

## Diagnosis
- all Canadian adults should have BP assessed at all appropriate clinical visits, oscillometric preferred to manual



**Suspect Hyperaldosteronism when**
- HTN refractory to treatment with ≥3 drugs
- Spontaneous hypokalemia
- Profound diuretic-induced hypokalemia (<3.0 mmol/L)
- Incidental adrenal adenomas



**Hypertensive Emergencies**
- **Malignant HTN**
- **Cerebrovascular**
  Hypertensive encephalopathy
  Stroke
  Intracerebral hemorrhage
  SAH
- **Cardiac**
  Acute aortic dissection
  Acute refractory LV failure
  Myocardial infarction/ischemia
  Acute pulmonary edema
- **Renal failure**

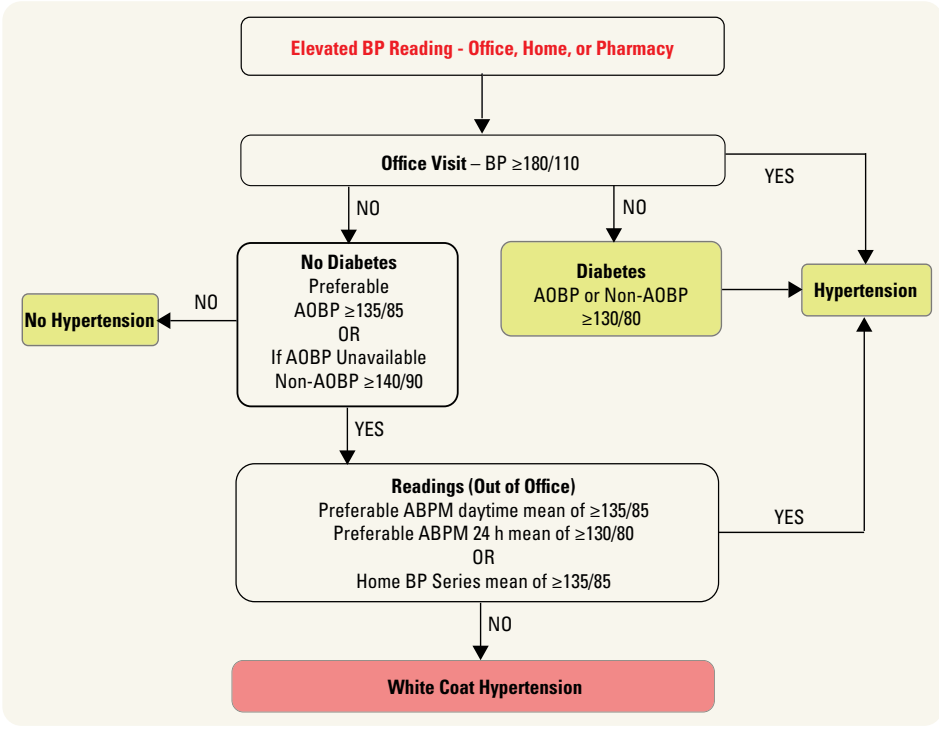



**Figure 12. Diagnostic algorithm for hypertension in adults**

## Treatment

- treat to target BP: <140/90 mmHg, <130/80 mmHg if DM
- optimum management of HTN requires assessment of overall cardiac risk
- adherence to lifestyle modification and pharmacotherapy should be assessed at each visit
- single pill combinations should be used as first line treatment (regardless of the extent of BP elevation)
- lifestyle modification (in all HTN patients – may be sufficient treatment in patients with stage 1 HTN (140-159/90-99))
  - diet
    - follow Canada's Guide to Healthy Eating (see *Nutrition*, FM9) and Dietary Approaches to Stop Hypertension (DASH)
    - limit daily sodium intake to 5 g or 87 mmol/d
    - potassium/magnesium/calcium supplementations are NOT recommended for HTN but an increase in dietary potassium may help
  - moderate intensity dynamic exercise: 30-60 min, 4-7x/wk; higher intensity exercise is not more effective
  - smoking cessation
  - low-risk alcohol consumption (see *Alcohol*, FM12)
  - work towards a healthy BMI (18.5-24.9 kg/m$^2$) and waist circumference (<102 cm for men, <88 cm for women)
  - individualized cognitive behavioural interventions for stress management
- pharmacological
  - indications for therapy (caution with elderly patients):
    - dBP ≥90 mmHg with target organ damage or independent cardiovascular risk factors
    - dBP ≥100 mmHg or sBP ≥160 mmHg without target organ damage or cardiovascular risk factors
    - sBP ≥140 with target organ damage
    - sBP >130 for high risk populations (Framingham Risk >20%, age >50)
  - first line antihypertensives (consider a single pill combination therapy)
  - combination therapy principles:
    - if there is an inadequate response to therapy, consider adding another first line antihypertensive
    - avoid combining a non-DHP CCB with a β-blocker or an ACEI with an ARB
    - monitor potassium and creatinine when administering an ACEI/ARB with a potassium sparing diuretic

**Impact of Health Behaviour on Blood Pressure**

| Intervention | Systolic BP (mmHg) | Diastolic BP (mmHg) |
|---|---|---|
| Diet and weight control | -6.0 | -4.8 |
| Reduced salt/ sodium intake | - 5.4 | - 2.8 |
| Reduced alcohol intake (heavy drinkers) | -3.4 | -3.4 |
| DASH diet | -11.4 | -5.5 |
| Physical activity | -3.1 | -1.8 |
| Relaxation therapies | -3.7 | -3.5 |

CHEP (Canadian Hypertension Education Program) Guidelines 2014. Available from: http://www.hypertension.ca/en/chep

**β-blocker**
Not recommended as first line for patients of age ≥60

**ACEI**
Not recommended as monotherapy in people of African descent

## Table 20. Considerations in the Individualization of Pharmacological Therapy in Adults

| Condition or Risk Factor | Recommended Drugs | Alternative Drugs | Not Recommended/Notes |
|---|---|---|---|
| **Isolated Diastolic HTN with or without Systolic HTN** | Monotherapy or SPC. Recommended monotherapy choices include thiazide/thiazide-like diuretics (with longer-acting diuretics preferred), ß-blockers, ACEI, ARBs, or long-acting CCBs. Recommended SPC choices include combinations of an ACEI with CCB, ARB with CCB, or ACEI/ARB with a diuretic. (Consider ASA and statins in selected patients) | Combinations of first-line drugs | Not recommended for monotherapy: α-blockers, β-blocker in those ≥60 yr of age, ACEI in black people. Hypokalemia should be avoided in those prescribed diuretics. ACEI, ARBs and direct renin inhibitors are potential teratogens, and caution is required if prescribing to women with childbearing potential. Combination of an ACEI with an ARB is not recommended |
| **Isolated Systolic HTN without other compelling indications** | Thiazide diuretic, ARB, or long acting dihydropyridine CCB | Combinations of first-line drugs | Same as above |
| **CAD** | ACEI or ARB; β-blockers or CCB for patients with stable angina | When combination therapy for high risk patients, ACEI/DHP CCB is preferred | Avoid short-acting nifedipine. Combination of an ACEI with an ARB is specifically not recommended. Exercise caution when lowering sBP to target if dBP is ≤60 mmHg, especially in patients with LVH |
| **Recent MI** | β-blocker and ACEI (ARB if cannot tolerate ACEI) | Long-acting CCB if β-blocker contraindicated or not effective. | Non-dihydropyridine CCBs should not be used with concomitant heart failure |
| **Left Ventricular Hypertrophy** | ACEI, ARB, thiazide/thiazide-like diuretics, or long-acting CCB | Combination of additional agents | Hydralazine and minoxidil can increase LVH, thus not recommended |
| **Cerebrovascular Disease (stroke/TIA)** | ACEI and thiazide/thiazide-like diuretic combination | Combination of additional agents | Treatment of HTN should not be routinely undertaken in acute stroke unless extreme BP elevation. ACEI and ARB combination after a stroke is not recommended |
| **Heart Failure** | ACEI (ARB if ACEI intolerant) and β-blockers<br>Aldosterone antagonists (mineralocorticoid receptor antagonists) may be added for patients with a recent cardiovascular hospitalization, acute myocardial infarction, elevated BNP or NT-proBNP level, or NYHA Class II to IV symptoms | ARB in addition to ACEI<br>Hydralazine/isosorbide dinitrate combination if ARB or ACEI not tolerated/contraindicated<br><br>Thiazide/thiazide-like or loop diuretics are recommended as additive therapy. DHP CCB can also be used<br><br>A combined ARB/neprilysin inhibitor is recommended (in place of an ACEI or ARB) in symptomatic patients with hypertension and HFrEF on standard guideline-based therapies | Titrate doses of ACEI and ARBs to those used in clinical trials. Carefully monitor potassium and renal function if combining any of ACEI, ARB and/or aldosterone antagonist |
| **Dyslipidemias** | Does not affect initial treatment recommendations | Combination of additional agents | |
| **DM with Albuminuria (ACR >2.0 mg/mmol renal disease, CVD or additional CV risk factors)** | ACEI or ARB | Addition of a dihydropyridine CCB is preferred over a thiazide/ thiazide-like diuretic | A loop diuretic could be considered in hypertensive chronic kidney disease patients with extracellular fluid volume overload |
| **DM without Albuminuria (criteria listed above)** | ACEI, ARB, DHP CCB, or thiazide/ thiazide-like diuretics | Combination of first-line drugs<br>If combination with ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/ thiazidelike diuretic | Normal urine microalbumin to creatinine ratio <2.0 mg/mmol |
| **Non-Diabetic Chronic Kidney Disease with Proteinuria (urinary protein >500 mg/24 h or ACR >30 mg/mmol)** | ACEI (ARB if ACEI intolerant), if there is proteinuria<br>Diuretics as additive therapy | Combinations of additional agents | Patients on an ACEI or ARB should have careful monitoring of renal function and potassium. ACEI and ARB combinations are not recommended in patients without proteinuria |
| **Renovascular Disease** | Does not affect initial treatment recommendations<br>Atherosclerotic renal artery stenosis should be primarily managed medically, while revascularization should be considered for renal fibromuscular dysplasia | Combinations of additional agents | Caution in using ACEI or ARB if bilateral renal artery stenosis or unilateral disease with solitary kidney<br>Renal artery angioplasty and stenting could be considered for patients with renal artery stenosis and complicated, uncontrolled hypertension |

2020 Hypertension Highlights, Hypertension Canada. https://hypertension.ca/wp-content/uploads/2018/07/Hypertension-Guidelines-English-2018-Web.pdf



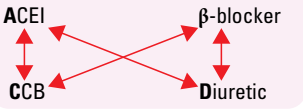
**Calcium Channel Blockers**

Dihydropyridine CCBs
- amlodipine
- nifedipine
- felodipine

Non-Dihydropyridine CCBs
- diltiazem
- verapamil



**How to Combine Antihypertensive Medications (in general)**






**Thiazides as First-Line Antihypertensive Therapy – ALLHAT**

JAMA 2002;288:2981-2997

**Purpose**: To evaluate whether calcium channel blocker or angiotensin-converting enzyme inhibitors lower incidence of coronary heart disease (CHD) or other cardiovascular disease (CVD) relative to treatment with a diuretic.

**Methods**: Randomized, double-blind, active-controlled clinical trial with mean follow-up of 4.9 yr. Participants with stage 1 or 2 hypertension (HTN) and at least 1 other CHD risk factor were included, and randomized to receive chlorthalidone (12.5-25 mg/d), amlodipine (2.5-10mg/d), or lisinopril (10-40 mg/d). Target BP was <140/90 mmHg, achieved by titrating the assigned study drug, and adding open-label agents when necessary. The primary outcome was combined fatal CHD or non-fatal MI. Secondary outcomes were all-cause mortality, stroke, combined CHD, and combined CVD.

**Results**: 33,357 participants (mean age 67 yr, 53% male, 47% white) were included. There were no significant differences in either the primary outcome or all-cause mortality between treatment groups. For amlodipine vs. chlorthalidone, secondary outcomes were similar except for a higher 6 yr rate of heart failure with amlodipine (10.2% vs. 7.7%; p<0.001). For lisinopril vs. chlorthalidone, lisinopril had higher 6 yr rates of combined CVD (33.3% vs. 30.9%; p<0.001), stroke (6.3% vs. 5.6%; p=0.02) and heart failure (8.7% vs. 7.7%; p<0.001).

**Conclusion**: Thiazide-type diuretics are superior to CCB and ACEI for preventing one or more major forms of CVD, with similar risks of death and non-fatal MI.

### Follow-Up
- assess and encourage adherence to pharmacological and non-pharmacological therapy at every visit
- lifestyle modification q3-6mo
- pharmacological
  - follow-up q1-2mo until BP under target for 2 consecutive visits. q3-6mo once at target BP
  - follow-up frequently for patients with symptomatic/severe HTN, antihypertensive drug intolerance, target organ damage
- referral is indicated for cases of refractory HTN, suspected secondary causes, or worsening renal failure
- hospitalization is indicated for malignant HTN

## Joint Pain

- see Rheumatology, RH3

### History
- number of joints involved: monoarticular, oligoarticular, polyarticular
- pattern of joints involved: symmetrical vs. asymmetrical, large vs. small joints, axial skeleton
- onset: acute vs. chronic (>6 wk)
- morning stiffness (duration) vs. worse at end of day with activity
- PMHx
  - trauma, infection, medications (steroids, diuretics)
  - comorbidities: DM, renal insufficiency (gout), psoriatic arthritis, myeloma, osteoporosis, and OA
  - FHx of arthritis, autoimmune disease
- ROS: constitutional symptoms (neoplasm, septic arthropathy), myalgia, skin/eye/nail/hand changes, and GI/GU changes

**Signs and Symptoms of Inflammatory Arthritis**

**WARM(S) Joints**
**W**orse with rest, better with activity
**A**wakening in the latter half of the night
**R**edness around joint
**M**orning stiffness (>30 min)
**S**oft tissue swelling, erythema

### Physical Exam
- vitals
- specific joint exams to affected areas
- systemic features (skin, nails, eyes, hands)

### Investigations (Guided by the History and Physical Exam)
- general: CBC and differential, electrolytes, Cr
- acute phase reactants: ESR, CRP
- complement (C3, C4)
- urinalysis to detect disease complications (proteinuria, active sediment)
- serology (ANA, anti-dsDNA, HLA-B27, anti-Jo-1, anti-Sm, anti-La, anti-Ro, RhF, and anti-CCP, etc.)
- synovial fluid analysis (cell count + differential, culture, Gram stain, microscopy)
- radiology (plain film, CT, MRI, U/S, bone densitometry, bone scan)

**Systemic Features**
- Fever (SLE, infection)
- Rash (SLE, psoriatic arthritis)
- Nail abnormalities (psoriatic, reactive arthritis)
- Uveitis (psoriatic, reactive arthritis, ankylosing spondylitis)
- Myalgias (fibromyalgia, myopathy)
- Weakness (polymyositis, neuropathy)
- GI symptoms (scleroderma, IBD)
- GU symptoms (reactive arthritis, gonococcemia)

### Treatment
- tailor therapy depending on the specific cause
- non-pharmacological: patient education, lifestyle modification, assisted devices, physiotherapy, occupational therapy
- pharmacological: analgesia (acetaminophen, NSAIDs), anti-inflammatory (DMARDs, steroids), antibiotics

## Low Back Pain

- see Orthopedic Surgery, OR26
- see CORE Back Tool: http://www.cfpc.ca/uploadedFiles/Resources/Resource_Items/Health_Professionals/CEP_CoreBackTool_2016.pdf

**Red Flags**
**B**owel or bladder dysfunction
**A**nesthesia (saddle)
**C**onstitutional symptoms/malignancy
**C**hronic disease
**P**aresthesias
**A**ge >50 and mild trauma
**I**V drug use/**I**nfection
**N**euromotor deficits

### Definition
- acute: <6 wk
- subacute: 6-12 wk
- chronic: >12 wk

### Epidemiology
- 5th most common reason for visiting a physician
- lifetime prevalence: 90%, and peak prevalence: age 45-60
- largest WSIB category and most common cause of chronic disability for individuals <45 yr old
- 90% resolve in 6 wk, <5% become chronic

## Etiology

- source of pain can be local, radicular, referred, or related to a psychiatric illness
- 98% are mechanical causes (worse with movement, better with rest)
  - soft tissue: sprain (ligament), strain (muscle)
  - spine: facet joint/disc degeneration, disc herniation, spinal stenosis (e.g. spondylosis), spondylolisthesis, compression fracture
  - other: pregnancy
- 2% are non-mechanical causes
  - surgical emergencies
    - cauda equina syndrome (areflexia, lower extremity weakness, saddle anesthesia, fecal incontinence, urinary retention)
- AAA (pulsatile abdominal mass)
  - medical conditions
- neoplastic: primary, metastatic, multiple myeloma
- infectious: osteomyelitis, TB
- metabolic: osteoporosis, osteomalacia, Paget's disease
- rheumatologic: ankylosing spondylitis, polymyalgia rheumatica
- referred pain: perforated ulcer, pancreatitis, pyelonephritis, ectopic pregnancy, herpes zoster

**Indications for Lumbar Spine X-Ray**

- No improvement after 6 wk
- Fever >38°C
- Unexplained weight loss
- Prolonged corticosteroid use
- Significant trauma
- Progressive neurological deficit
- Suspicion of ankylosing spondylitis
- History of cancer (rule out metastases)
- Alcohol/drug abuse (increased risk of osteomyelitis, trauma, fracture)

## Physical Exam

- inspection: curvature, posture, gait
- palpation: bony deformities/tenderness, paraspinal muscle bulk/tenderness, trigger points
  - percussion of spine to elicit pain due to fracture or infection
- range of motion and peripheral pulses
- neurologic exam for L4/L5/S1 helps determine level of spinal involvement (power, reflexes, sensation)
- special tests
  - straight leg raise (positive if pain at <70 degrees and aggravated by ankle dorsiflexion), positive test is indicative of sciatica
  - crossed straight leg raise (raising of uninvolved leg elicits pain in leg with sciatica), more specific than straight leg raise
  - femoral stretch test (patient prone, knee flexed, examiner extends hip) to diagnose L4 radiculopathy

## Investigations

- plain films not recommended in initial evaluation
- if infection/cancer suspected: CBC, ESR
- if neurologic deficits worsening or infection/cancer suspected: consider CT or MRI

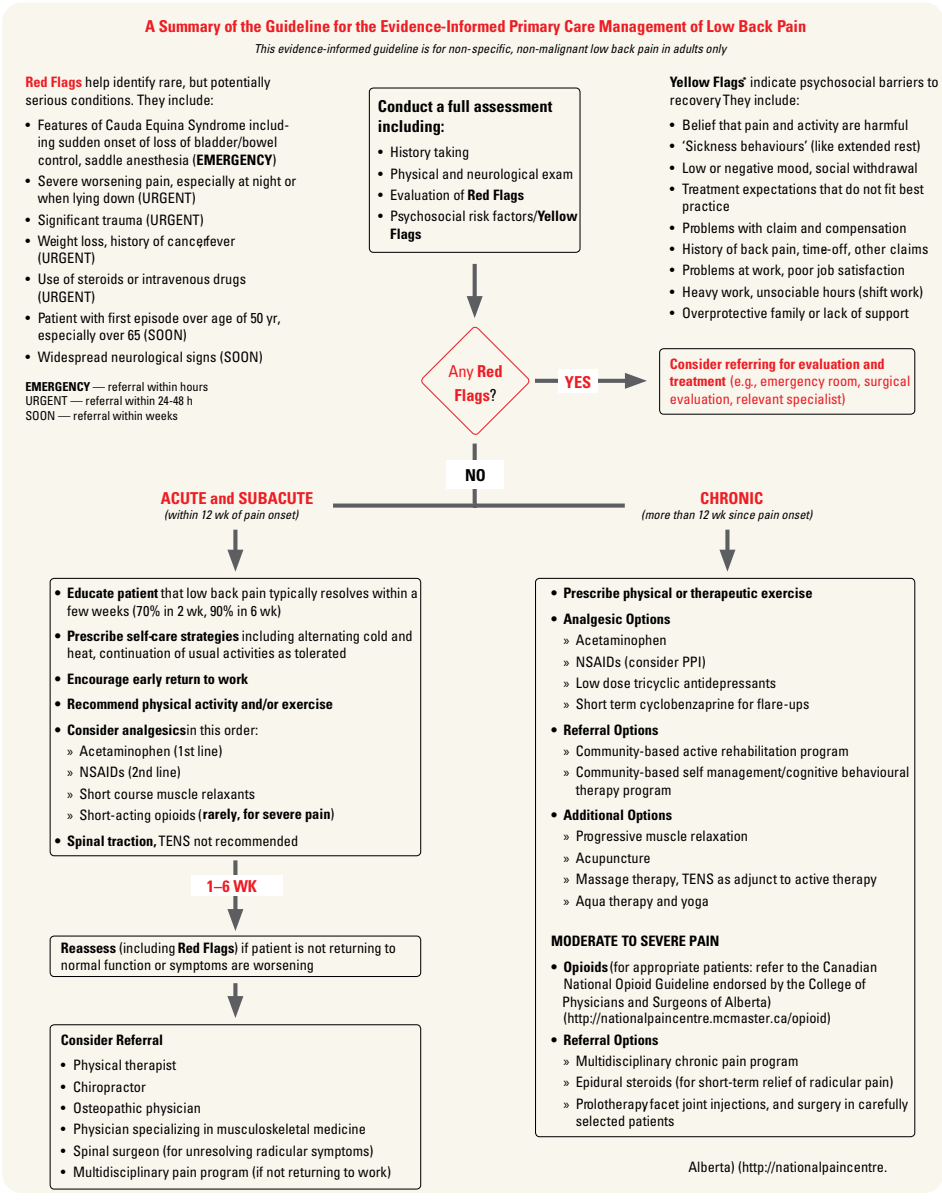



**Figure 13. Low back pain treatment**
Reprinted with permission from: Kendall NAS, et al. Guide to Assessing Psycho-Social Yellow Flags in Acute Low Back Pain. ACC & NZGG, Wellington, NZ. (2004 ed.); Toward Optimized Practice. Guideline for the evidence-informed primary care management of low back pain, 2nd ed. 2007. Available from: www.topalbertadoctors.org

**Massage for Low Back Pain**
Cochrane DB Syst Rev 2015;4:CD001929
**Purpose**: To evaluate the effect of massage therapy for non-specific low back pain.
**Methods**: Meta-analysis of randomized or quasi-randomized trials evaluating use of any massage modality (hands or mechanical device) as a treatment for non-specific low back pain.
**Results**: 13 RCTs were identified, comparing massage therapy to other active or sham treatments. Massage was superior for pain and function on both short and long-term follow-ups relative to sham treatment. It was similar to exercises, and superior to join mobilization, relaxation therapy, physical therapy, acupuncture and self-care education. Benefits lasted at least 1 yr post-treatment. Acupuncture massage was associated with better results than classic (Swedish) massage, and Thai massage produced similar results to the classic massage.
**Conclusions**: Massage may be beneficial for subacute and chronic non-specific low back pain, especially in combination with exercise and education; it is more effective than classic massage.

**Spinal Manipulative Therapy (SMT) for Acute Low-Back Pain**
Cochrane DB Syst Rev 2012;9:CD008880
**Purpose**: To evaluate spinal manipulative therapy (SMT) for acute low back pain.
**Methods**: Meta-analysis of RCTs examining effectiveness of SMT (hands-on therapy directed towards spine, including both manipulation and mobilization) in adults with acute low back pain (pain lasting <6 wk). Studies involving patients with predominantly low back pain but radiating into the buttocks and legs were also included. Primary outcomes were back pain, back-pain specific functional status and perceived recovery.
**Results**: 20 RCTs involving 2674 participants were included. Low to very low quality evidence suggested no difference in effect for SMT compared to inert interventions, sham SMT or as an adjunct to another intervention, for the primary outcomes. Side-lying and supine thrust SMT techniques demonstrated a short-term significant difference when compared to non-thrust SMT techniques for outcomes of pain, functional status and recovery.
**Conclusion**: SMT is not more effective than inert interventions, sham SMT or as an adjunct to another intervention for patients with acute low back pain, and does not appear any better than other recommended therapies either. Decision to refer patients for SMT should be based on costs, patient and provider preferences, and the relative safety of SMT relative to other treatment options.

## Table 21. Approach to Non-Traumatic Low Back Pain

| | **Back Dominant** (Pain greatest above gluteal fold) | | **Leg Dominant** (Pain greatest below gluteal fold) | |
|---|---|---|---|---|
| **History** | **Pattern 1**<br>Worse with flexion<br>Constant/intermittent | **Pattern 2**<br>Worse with extension<br>Never worse with flexion<br>Always intermittent | **Pattern 3**<br>Pain changes with back movement/position<br>Currently/previously constant | **Pattern 4**<br>Worse with activity<br>Improves with rest and posture change<br>Intermittent/short duration |
| **Physical Exam** | Normal neuro exam<br>Fast responder<br>Improves with extension<br>Slow responder<br>No change or worsens with extension | Normal neuro exam<br>± improves with flexion<br>Worse with extension | Leg pain can improve but not disappear<br>Positive straight leg raise ± conduction loss<br>Fast responder<br>Improves with specific back position<br>Slow responder<br>Not better with position changes | No irritative findings ± conduction loss |
| **Likely Pathology** | Disc pain | Facet joint pain | Compressed nerve pain: sciatica | Symptomatic spinal stenosis: neurogenic claudication |
| **Initial Management** | Scheduled extension<br>Lumbar roll<br>Night lumbar roll<br>Medication as required: acetaminophen + NSAIDs | Scheduled flexion<br>Limited extension<br>Night lumbar roll<br>Medication as required: acetaminophen + NSAIDs | Prone extension<br>Supine "Z" lie<br>Lumbar roll<br>Night lumbar roll<br>Medication as required: acetaminophen + NSAIDs, may consider if 1st line not sufficient | Abdominal exercises<br>Night lumbar roll<br>Sustained flexion<br>Pelvic tilt<br>Medication as required: acetaminophen + NSAIDs |

Adapted from: American Academy of Orthopaedic Surgeons. Acute care: nontraumatic low back pain. Orthopaedic Knowledge Update: Spine 2 2001;153-166
Adapted from: Centre for Effective Practice. Clinically Organized Relevant Exam (CORE) Back Tool. 2016

# Menopause/Hormone Replacement Therapy

• see Gynecology, GY33

### Epidemiology
- mean age of menopause = 51.4 yr

### Clinical Features
- associated with estrogen deprivation
- urogenital tract: atrophy, vaginal dryness/itching, urinary frequency/urgency/incontinence, bleeding
- vascular: vasomotor instability (e.g. hot flashes), increased risk of heart disease
- bones: bone loss, joint/muscle/back pain, fractures, loss of height
- brain: depression, irritability, mood swings, memory loss

### Management
- non-pharmacological management: encourage physical exercise, smoking cessation, and a balanced diet with adequate intake/supplementation of calcium (1200 mg/d) and vitamin D (1000 IU/d)
- pharmacological management:
  - hormone replacement therapy (HRT)
    - initiation of HRT requires a thorough discussion of short- and long-term benefits and risks
    - prescribe for moderate to severe symptoms for no longer than 5 yr; routine use is not recommended
    - regimens: cyclic or continuous estrogen-progestin, estrogen only (if no uterus, patch/gel/cream/ring/vaginal tablet)
    - advantages: decreases risk of osteoporotic fractures, colorectal cancer
    - disadvantages: increases risk of breast cancer, coronary heart disease, stroke, DVT, and PE
  - venlafaxine, SSRIs, or gabapentin to ease vasomotor instability

# Osteoarthritis

• see Rheumatology, RH5

### Epidemiology
- most common form of arthritis seen in primary care
- prevalence is 10-12% and increases with age
- results in long-term disability in 2-3% of patients with OA
- almost everyone over the age of 65 shows signs of OA on x-ray, but only 33% of these individuals will be symptomatic

### Clinical Features
- joint pain with activity, improved with rest, morning stiffness or gelling <30 min
- deformity, bony enlargement, crepitus, limitation of movement, peri-articular muscle atrophy
- usually affects distal joints of hands, spine, hips, and knees

### Investigations
- no laboratory tests for the diagnosis of OA
- hallmark radiographic features: joint space narrowing, subchondral sclerosis, subchondral cysts, osteophytes

### Management
- goals: relieve pain, preserve joint motion and function, prevent further injury
- conservative
  - patient education, weight loss, low-impact exercise (OT/PT), assistive devices (e.g. canes, orthotics)
- pharmacological
  - consider comorbidities such as PUD, HTN, IHD, hepatic disease, and renal disease
  - medications do not alter natural course of OA
  - 1st line: acetaminophen up to 4 g/d (OA is not an inflammatory disorder)
  - 2nd line: NSAIDs (COX-2 selective) in low doses for short durations
  - 3rd line: combination analgesics (e.g. acetaminophen and codeine)
  - other pharmacological adjuncts:
    - intra-articular corticosteroid or hyaluronic acid injections
    - topical NSAIDS (diclofenac)
    - capsaicin cream
    - oral glucosamine
- surgery
  - consider if persistent significant pain and functional impairment despite optimal pharmacotherapy (e.g. debridement, osteotomy, total joint arthroplasty)

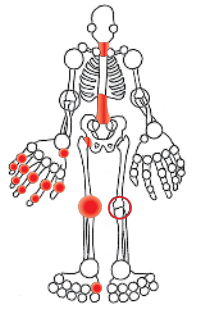



**Figure 14. Common sites of involvement in OA**

# Osteoporosis

• see Endocrinology, E43

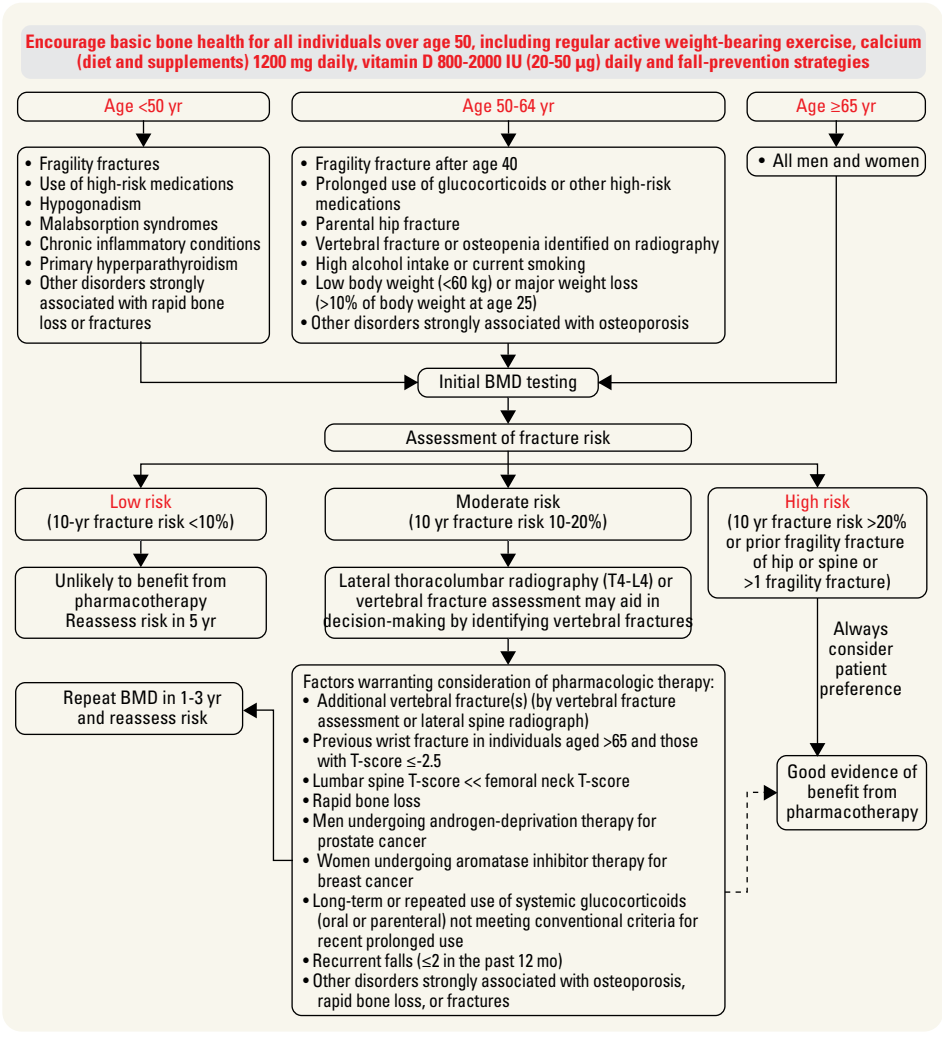



**Figure 15. 2010 Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada**
(integrated management model) Adapted from: CMAJ 2010;182:1864-1873

## Epidemiology

- for current guidelines and tools see www.osteoporosis.ca
- age-related disease characterized by decreased bone mass and increased susceptibility to fractures
- affects 1 in 4 Canadian women and 1 in 8 Canadian men

## Approach to Clinical Assessment

- identify risk factors on history and physical examination
  - history
- prior falls, fragility fractures, parental hip fractures, and gait or balance issues
- glucocorticoid use
- smoking and alcohol intake (≥3 units/d)
- rheumatoid arthritis
  - physical examination
    - height annually (prospective loss >2 cm or historical loss >6 cm) and weight (weight loss >10% since age 25)
    - rib-to-pelvis distance ≤2 fingers' breadth
    - occiput-to-wall distance >5 cm
    - assess fall risk by ability to get up from chair without support with arms, and walking several steps and return

**Disorders Strongly Associated with Osteoporosis Include:**
Primary hyperparathyroidism, type 1 DM, osteogenesis imperfecta, uncontrolled hyperthyroidism, hypogonadism or premature menopause (<45 yr), Cushing's disease, chronic malnutrition or malabsorption, chronic liver disease, COPD, and chronic inflammatory conditions (e.g. IBD)

**10 Yr Fracture Risk Assessment**
FRAX (WHO Fracture Risk Assessment Tool) and CAROC (Canadian Association of Radiologists and Osteoporosis Canada) have been validated in the Canadian Population
FRAX and CAROC are available online from: https://www.osteoporosis.ca/health-care-professionals/clinical-tools-and-resources/

**How Much Calcium Do We Need?**

| Age | |
|---|---|
| 4-8 | 1000 mg |
| 9-18 | 1300 mg |
| 19-50 | 1200 mg |
| >50 | 1200 mg |
| Pregnant and lactating women 19-50 | 1000 mg |

**Calcium Content of Common Foods**
- 1 cup milk = 300 mg
- ¾ cup yogurt = 332 mg
- ½ can salmon with bones = 240 mg
- ½ cup cooked broccoli = 33 mg
- 1 medium orange = 50 mg

**Vitamin D Content in Food**
- Milk fortified with vitamin $D_3$ contains 100 IUs per 250 mL glass
- Foods such as margarine, eggs, chicken livers, salmon, sardines, herring, mackerel, swordfish, and fish oils (halibut and cod liver oils) all contain small amounts; supplementation is necessary to obtain adequate levels as dietary intake has minimal impact
- Most multivitamins provide 400 IUs of vitamin $D_3$

### Investigations
- CBC, Cr, corrected $Ca^{2+}$, ALP, TSH, 25-OH-D (after 3-4 mo of adequate supplementation), and serum protein electrophoresis if there are vertebral fractures

### Indications for Bone Mineral Density Testing and Management
- see Endocrinology, E43

# Rash

- see Dermatology, D13

# Sexually Transmitted Infections

- see Gynecology, GY26

### Definition
- diverse group of infections caused by multiple microbial pathogens
- transmitted by either secretions or fluids from mucosal surfaces

### Epidemiology
- high incidence rates worldwide
- Canadian prevalence in clinical practice
  - common: chlamydia (most common), gonorrhea (2nd most common), HPV, genital herpes
  - less common: hepatitis B, HIV, syphilis, trichomoniasis
  - rare: chancroid, granuloma inguinale, lymphogranuloma venereum
- non-sexually transmitted genital tract infections: vulvovaginal candidiasis (VVC), bacterial vaginosis (BV)
- three most common infections associated with vaginal discharge in adult women are BV, VVC, and trichomoniasis

### History
- sexual history
  - age of first intercourse, sexual orientation, sexual activity (oral, anal, and/or vaginal intercourse), sexual activity during travel
  - total number of partners in the past year/month/week and duration of involvement with each
- STI history
  - STI awareness, contraception, previous STIs and testing (including Pap tests), partner communication regarding STIs
  - local symptoms such as burning, itching, discharge, sores, vesicles, testicular pain, dysuria, abdominal pain
  - systemic symptoms such as fever, lymphadenopathy, arthralgia

### Investigations/Screening
- individuals at increased risk should be screened for chlamydia, gonorrhea, hepatitis B, HIV, and syphilis
- Pap test if none performed in preceding 3 yr

### Management
- primary prevention is vastly more effective than treating STIs and their sequelae
- offer hepatitis B vaccine if not immune
- offer Gardasil® to women over 9 yr
- discuss STI risk factors (e.g. decreasing the number of sexual partners)
- direct advice to ALWAYS use condoms or to abstain from intercourse
- condoms are not 100% effective against HPV or HSV
- an STI patient is not considered treated until the management of his/her partner(s) is ensured (contact tracing by Public Health)
- patients diagnosed with bacterial STI or trichomonal infection should abstain from sexual activity until treatment completion and for 7 d after treatment for both partners, or until test of cure completed
- mandatory reporting: chlamydia, gonorrhea, hepatitis B, HIV, syphilis





When an STI is detected in a child, evaluation for sexual abuse is mandatory



**STI Risk Factors**
- Sexually active males and females <25 yr old
- Unprotected sex, sexual contact with a known case of STI, previous STI
- New sexual partner or >2 sexual partners in the past 12 mo
- Street involved, homeless, and/or substance abuse



**Sexual History**
**5 P's**
**P**artners (numbers, gender)
**P**ractices (vaginal, oral, anal insertive/receptive)
**P**rotection
**P**ast history of STIs
**P**regnancy prevention



**Efficacy of Human Papillomavirus Vaccines – A Systematic Quantitative Review**
Int J Gynecol Cancer 2009;19:1166-1176
**Purpose**: To evaluate two vaccines for human papillomavirus (HPV) in terms of efficacy, safety and immunogenicity.
**Methods**: Systematic review of RCTs involving women between the ages of 9 and 26 yr, randomly assigned to receive vaccination with HPV L1 virus-like particle in either quadrivalent (HPV 6, 11, 16, 18), bivalent (HPV 16, 18), or univalent (HPV 16) form or placebo. Main outcomes were prevention of cytologically and/or histologically proven lesions (including LSIL, HSIL, VIN, VAIN, AIN, adenocarcinoma in situ of the cervix, or cancer of the cervix associated with HPV infection).
**Results**: Six studies involving 47,236 women were included. Bivalent and quadrivalent vaccines reduced the rate of lesions in the cervix, vulva, vagina, and anogenital region with efficacy of 93% (95% CI 87-96%) and 62% (95% CI 27-70), respectively. More symptoms were found in the bivalent vaccine group (35%, 5-73%) compared to control groups.
**Conclusion**: Prophylactic vaccination can prevent HPV infection in women aged 9 to 26 yr not previously infected with HPV subtypes covered by the vaccines.

**Table 22. Diagnosis and Treatment of Common STIs**

| | Signs and Symptoms | Investigations | Treatment | Complications |
|---|---|---|---|---|
| **Gonococcal Urethritis/ Cervicitis** (*Neisseria gonorrhoeae*) | M: urethral discharge, unexplained pyuria, dysuria, irritation, testicular swelling, Sx of epididymitis<br><br>F: mucopurulent endocervical discharge, vaginal bleeding, dysuria, pelvic pain, dyspareunia<br><br>M and F: often asymptomatic, can involve rectal symptoms in cases of unprotected anal sex | M: urethral swab for Gram stain and culture<br><br>F: urine PCR, endocervical swab for Gram stain and culture, vaginal swab for wet mount (to rule out trichomonas)<br><br>M and F: urine PCR, rectal/ pharyngeal swabs if indicated | Ceftriaxone 250 mg IM single dose*<br>If risk factors for treatment failure (e.g. pregnancy, pharyngeal/rectal infection, potentially reduced susceptibility)<br>Test of cure: culture 4 d post-treatment (preferred) or urine PCR 2 wk post treatment (alternative)<br>If no risk factors, rescreen 6-12 mo post treatment | M: urethral strictures, epididymitis, infertility<br><br>F: PID, infertility, ectopic pregnancy, perinatal infection, chronic pelvic pain<br><br>M and F: Arthritis, increased risk of acquiring and transmitting HIV |
| **Non-Gonococcal Urethritis/Cervicitis** (Usually *Chlamydia trachomatis***) | ~70% asymptomatic<br>If symptoms appear (usually 2-6 wk after infection) then similar to gonococcal symptoms (see above) | Same as above | Azithromycin 1 g PO single dose + gonococcal urethritis/cervicitis Rx*<br>Same follow-up as above | Same as above |
| **Human Papillomavirus** (genital warts, cervical dysplasia) | Most are asymptomatic<br>M: cauliflower lesions (condylomata acuminata) on skin/mucosa of penile or anal area<br><br>F: cauliflower lesions and/or pre-neoplastic/neoplastic lesions on cervix/vagina/vulva | None needed if simple condylomata<br>Potential biopsy of suspicious lesions<br><br>F: screening for cervical dysplasia through regular Pap smears | For condylomata: cryotherapy, electrocautery, laser excision, topical therapy (patient-applied or office-based)<br>For cervical dysplasia: colposcopy and possible excision, dependent on grade of lesion | M and F: anal cancer MSM and F who have receptive anal sex: rectal cancer<br><br>F: cervical/vaginal/vulvar cancer |
| **Genital Herpes** (HSV-1 and -2) | 1° episode: painful vesicoulcerative genital lesions ± fever, tender lymphadenopathy, protracted course<br>Recurrent episodes: less extensive lesions, shorter course may have "trigger factors" | Swab of vesicular content for culture, type-specific serologic testing for HSV-1 vs. HSV-2 antibodies and to determine 1° vs. recurrent episode | 1° Episode<br>Acyclovir 200 mg PO 5x/d x 5-10 d or<br>Famciclovir 250 mg PO tid x 5 d or<br>Valacyclovir 1000 mg PO bid x 10 d<br><br>Recurrent Episode<br>Acyclovir 200 mg PO 5x/d x 5d or 800 mg PO tid x 2 d or<br>Famciclovir 125 mg PO bid x 5 d or<br>Valacyclovir 500 mg PO bid x 3 d or 1000 mg PO OD x 3 d | Genital pain, urethritis, cervicitis, aseptic meningitis, increased risk of acquiring and transmitting HIV |
| **Infectious Syphilis** (*Treponema pallidum*) | 1°: chancre (painless sore), regional lymphadenopathy<br>2°: rash and flu-like symptoms, meningitis, headache, uveitis, retinitis, condyloma lata, mucus lesions, alopecia<br>Latent Phase: asymptomatic<br>3°: neurologic, cardiovascular, and tissue complications | Specimen collection from 1° and 2° lesions, screen high risk individuals with serologic syphilis testing (VDRL), universal screening of pregnant women | Benzathine penicillin G IM (dose depends on stage and patient population. Check Public Health Canada guidelines )<br>Notify partners (last 3-12 mo)<br>Continuous follow-up and testing until patients are seronegative | Chronic neurologic and cardiovascular sequelae, increased risk of acquiring and transmitting HIV |

F = females; M = males
*N.B. if urethritis/cervicitis is suspected, always treat for both gonococcal and non-gonococcal types (i.e. ceftriaxone AND azithromycin)
**Most common reportable STI in Canada

# Sinusitis

- see Otolaryngology, OT24

## Etiology

- viral etiology is more common
- viral: rhinovirus, influenza, parainfluenza
- bacterial: *S. pneumoniae, H. influenzae, M. catarrhalis*

## Management of Acute Sinusitis

- for symptom relief: oral analgesics (acetaminophen, NSAIDs), nasal saline rinse, short-term use of topical/ or oral decongestants
- do not prescribe antihistamines
- mild to moderate acute bacterial sinusitis: intra-nasal corticosteroids
- severe acute bacterial sinusitis: antibiotics and intra-nasal corticosteroids
  - first-line antibiotic is amoxicillin, and second line is amoxicillin-clavulanic acid or a fluoroquinolone
  - ENT referral if: anatomic defect (e.g. deviated septum, polyp, adenoid hypertrophy), failure of second-line therapy, or ≥4 episodes/yr, refer urgently when there is development of complications (e.g. orbital extension, meningitis, intra-cranial abscess, venous sinus thrombosis), altered mental status, headache, systemic toxicity, or neurological findings



**Red Flags for Urgent Referral**
- Altered mental status
- Headache
- Systemic toxicity
- Swelling of the orbit or change in visual acuity or extraocular muscles
- Hard neurological findings
- Signs of meningeal irritation
- Suspected intra-cranial complications (meningitis, intra-cranial abscess, cavernous sinus thrombosis)
- Involvement of associated structures (periorbital cellulitis, Pott's puffy tumour)

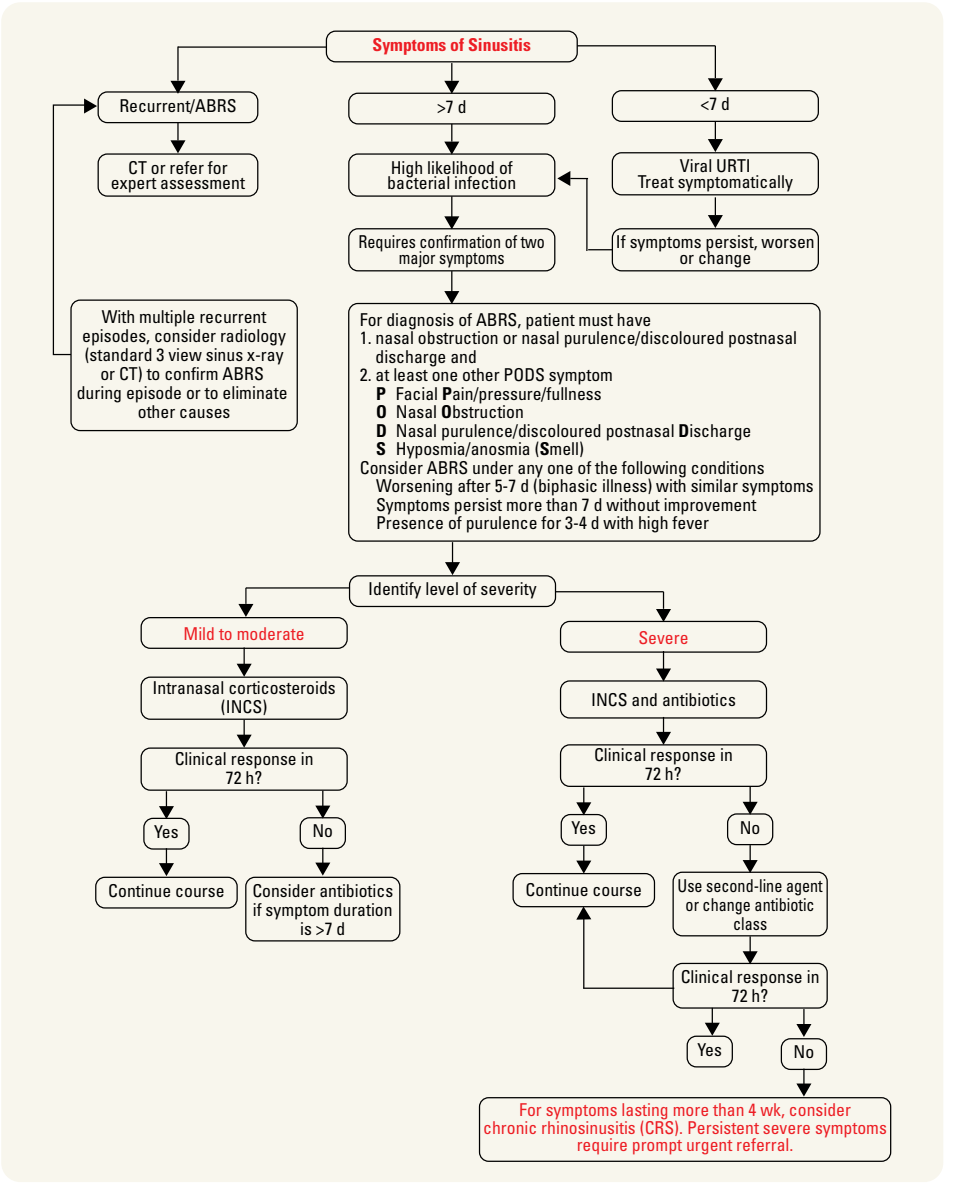



**Figure 16. Diagnosis and management of sinusitis**
ABRS = acute bacterial rhinosinusitis
Adapted from: Desrosiers M, et al. Allergy Asthma Clin Immunol 2011;7:doi:10.1186/1710-1492-7-2

# Sleep Disorders



- see Respirology, R28 and Neurology, N46

## Definition

- most often characterized by one of three complaints
  - insomnia
- difficulty falling asleep, difficulty maintaining sleep, early morning wakening, non-refreshing sleep
  - parasomnias
- night terrors, nightmares, restless leg syndrome, somnambulism (performing complex behaviour during sleep with eyes open but without memory of event)
  - excessive daytime sleepiness

## Epidemiology

- 1/3 of patients in primary care setting have occasional sleep problems, 10% have chronic sleep problems

## Etiology

- primary sleep disorders
  - primary insomnia, narcolepsy, obstructive sleep apnea, restless leg syndrome, periodic limb movements of sleep
- secondary causes
  - medical: COPD, asthma, CHF, hyperthyroidism, chronic pain, BPH, menopause, GERD, PUD, pregnancy, neurological disorders

- drugs: alcohol, caffeine, nicotine, nicotine replacement therapy, β-agonists, antidepressants, steroids
- psychiatric: mood and anxiety disorders
- lifestyle factors: shift work, jet-lag

## Investigations

- complete sleep diary every morning for 1-2 wk
  - record bedtime, sleep latency, total sleep time, awakenings, quality of sleep
- rule out specific medical problems (e.g. CBC and differential, TSH)
- refer for sleep study, nocturnal polysomnogram, or daytime multiple sleep latency test if suspicion of sleep apnea or periodic leg movements of sleep

## Management of Specific Problems

- **Primary Insomnia**
  - person reacts to insomnia with fear or anxiety around bedtime or with a change in sleep hygiene, which can progress to a chronic disorder (psychophysiological insomnia)
  - treat any suspected medical or psychiatric cause
  - exercise regularly, avoid heavy exercise within 3 h of bedtime
  - first-line treatment (CBT)
    - sleep hygiene: avoid alcohol, caffeine, nicotine; comfortable sleep environment; regular sleep schedule; no napping
    - relaxation therapy: deep breathing, meditation, biofeedback
    - stimulus control therapy: re-association of bed/bedroom with sleep, re-establishment of a consistent sleep-wake schedule, reduce activities that cue staying awake
    - sleep restriction therapy: total time in bed should closely match the total sleep time of the patient
    - address inappropriate beliefs and attitudes that perpetuate dysfunctional sleep
  - pharmacologic treatment (used to supplement CBT; short-term prescription of <14 d with appropriate follow-up in 7-14 d):
    - short-acting benzodiazepines (e.g. lorazepam) are used to:
      - break the cycle of chronic insomnia
      - manage an exacerbation of previously controlled insomnia
    - non-benzodiazepines: zoplicone, zolpidem, melatonin, sedating anti-depressants (e.g. amitriptyline, trazadone)
    - if no progress or limited improvement on pharmacotherapy, consider referral to sleep medicine program
  - other treatment: exercise regularly, avoid heavy exercise within 3 h of bedtime
- **Snoring**
  - results from soft tissue vibration at the back of the nose and throat due to turbulent airflow through narrowed air passages
  - physical exam: obesity, nasal polyps, septal deviation, hypertrophy of the nasal turbinates, enlarged uvula and tonsils
  - investigations (only if severely symptomatic): nocturnal polysomnography and airway assessment (CT/MRI)
  - treatment
    - sleep on side (position therapy), weight loss
    - nasal dilators, tongue-retaining devices, mandibular advancement devices
  - at risk of developing obstructive sleep apnea
- **Obstructive Sleep Apnea (OSA)**
  - apnea (no breathing for ≥10 s) resulting from partial or complete upper airway obstruction due to collapse of the base of the tongue, soft palate with uvula, and epiglottis; respiratory effort is present
  - leads to a distinctive snorting, choking, awakening type pattern as the body rouses itself to open the airway
  - apneic episodes can last from 20 s-3 min and occur 100-600 episodes/night
  - diagnosis is based on nocturnal polysomnography: >15 apneic/hypopneic episodes per hour of sleep
  - consequences
    - daytime somnolence, non-restorative sleep
    - poor social and work performance
    - mood changes: anxiety, irritability, depression
    - sexual dysfunction: poor libido, impotence
    - morning headache (due to hypercapnia)
    - HTN (2x increased risk), CAD (3x increased risk), stroke (4x increased risk), arrhythmias
    - OSA is an independent risk factor for CAD
    - pulmonary HTN, right ventricular dysfunction, cor pulmonale (due to chronic hypoxemia)
    - memory loss, decreased concentration, confusion
  - investigations
    - evaluate BP, inspect nose, and oropharynx (enlarged adenoids or tonsils)
    - blood gas not helpful, TSH if clinically indicated
    - nocturnal polysomnography
  - treatment
    - modifiable factors: avoid sleeping supine; weight loss; avoid alcohol, sedatives, opioids; inhaled steroids if nasal swelling present; dental appliances to modify mandibular position
    - primary treatment of OSA is CPAP: maintains patent airway in 95% of OSA cases
    - surgery: somnoplasty, uvulopalatopharyngoplasty (UPPP), tonsillectomy, and adenoidectomy (in children)
    - report patient to Ministry of Transportation if OSA is not controlled by CPAP



**Risk Factors for Obstructive Sleep Apnea**

- 2% of women, 4% of men between ages 30-60
- Obesity (due to upper airway narrowing). BMI >28 kg/m$^2$ present in 60-90% of cases
- Children (commonly due to large tonsils and adenoids)
- Aging (due to decreased muscle tone)
- Persistent URTIs, allergies, nasal tumours, hypothyroidism (due to macroglossia), neuromuscular disease
- Family history

# Sore Throat (Pharyngitis)

## Definition
- inflammation of the oropharynx
- may be caused by a wide range of infectious organisms, most of which produce a self-limited infection with no significant sequelae

## Etiology
- viral: adenovirus, rhinovirus, influenza virus, RSV, EBV, coxsackie virus, herpes simplex virus, CMV, HIV
- bacterial: Group A β-Hemolytic *Streptococcus* (GABHS), Group C and Group β-Hemolytic *Streptococcus, Neisseria gonorrhoeae, Chlamydia pneumoniae, Mycoplasma pneumoniae, Corynebacterium diphtheriae*

## Epidemiology
- viral
  - most common cause (90% in adults is viral), occurs year round
- bacterial
  - GABHS (Group A β-Hemolytic Streptococcal Infections)
    - most common bacterial cause
    - occurs most often in winter months
    - 5-15% of adult cases and up to 50% of all pediatric cases of acute pharyngitis
    - most prevalent between 5-17 yr old

## Clinical Features
- viral
  - pharyngitis, conjunctivitis, rhinorrhea, hoarseness, cough
  - nonspecific flu-like symptoms such as fever, malaise, and myalgia
  - often mimics bacterial infection
  - common viral infections
    - EBV (infectious mononucleosis)
      - pharyngitis, tonsillar exudate, fever, lymphadenopathy, fatigue, rash
    - coxsackie virus (hand, foot, and mouth disease)
      - primarily late summer, early fall
      - sudden onset of fever, pharyngitis, headache, abdominal pain, and vomiting
      - appearance of small vesicles that rupture and ulcerate on soft palate, tonsils, pharynx
      - ulcers are pale grey and several mm in diameter, have surrounding erythema, and may appear on hands and feet
    - herpes simplex virus
      - like coxsackie virus but ulcers are fewer and larger
      - pharyngitis, tonsillar exudate, fever, lymphadenopathy, fatigue, rash
- bacterial
  - symptoms: pharyngitis, fever, malaise, headache, abdominal pain, absence of cough
  - signs: fever, tonsillar or pharyngeal erythema/exudate, swollen/tender anterior cervical nodes, halitosis
  - complications:
    - suppurative: abscess, sinusitis, otitis media, cervical adenitis, pneumonia
    - non-suppurative: acute rheumatic fever, acute glomerulonephritis

## Investigations
- suspected GABHS
  - see Table 23 for approach to diagnosis and management of GABHS
  - gold standard for diagnosis is throat culture
  - rapid test for streptococcal antigen: high specificity (95%) but low sensitivity (50-90%)
  - suspected EBV (infectious mononucleosis)
- peripheral blood smear, heterophile antibody test (i.e. the latex agglutination assay or "monospot")

**Red Flags in Patients with "Sore Throat"**
- Persistence of symptoms longer than 1 wk without improvement
- Respiratory difficulty (particularly stridor, croup, etc.)
- Difficulty in handling secretions (peritonsillar abscess)
- Difficulty in swallowing (Ludwig's angina)
- Severe pain in the absence of erythema (supraglottitis/epiglottitis)
- Palpable mass (neoplasm)
- Blood in the pharynx or ear (trauma)

**Table 23. Modified Centor Score: Approach to Diagnosis and Management of GABHS**

| | POINTS |
|---|---|
| Cough absent? | 1 |
| History of fever >38°C? | 1 |
| Tonsillar exudate? | 1 |
| Swollen, tender anterior nodes? | 1 |
| Age 3-14 | 1 |
| Age 15-44 | 0 |
| Age >45 | –1 |

In communities with moderate levels of strep infection (10-20% of sore throats):

| Score | 0 | 1 | 2 | 3 | 4 or more |
|---|---|---|---|---|---|
| Chance patient has strep | 1-2.5% | 5-10% | 11-17% | 28-35% | 51-53% |
| Suggested action | NO culture or antibiotic | | Culture all, treat with antibiotics only if culture is positive | | Culture all, treat with antibiotics on clinical grounds[1], discontinue antibiotics if culture comes back negative |

[1]Clinical grounds include a high fever or other indicators that the patient is clinically unwell and is presenting early in the course of the illness
Limitations: *This score is not applicable to patients <3 yr of age
*If an outbreak or epidemic of illness caused by GABHS is occurring in any community, the score is invalid and should not be used
Adapted from: Centor RM, et al. Med Decis Making 1981;1:239-46; McIssac WI, et al. *CMAJ* 1998;158:75-83

### Management
- viral pharyngitis
  - antibiotics not indicated
  - symptomatic therapy: acetaminophen/NSAIDs for fever and muscle aches, decongestants
- GABHS
  - antibiotic treatment decreases severity and duration of symptoms, risk of transmission (after 24 h of treatment), and risk of rheumatic fever and suppurative complications
  - 10 d of treatment required
  - incidence of glomerulonephritis is not decreased with antibiotic treatment
  - no increased incidence of rheumatic fever with 48 h delay in antibiotic treatment; if possible, delay antibiotic treatment until culture confirms diagnosis
  - routine F/U and/or post-treatment throat cultures are not required for most patients
  - F/U throat culture only recommended for: patients with history of rheumatic fever, patients of family member(s) with history of acute rheumatic fever, suspected streptococcal carrier
- infectious mononucleosis (EBV)
  - self-limiting course; antibiotics are not indicated
  - symptomatic treatment: acetaminophen/NSAIDs for fever, pharyngitis, malaise
  - avoid heavy physical activity and contact sports for at least 1 mo or until splenomegaly resolves because of risk of splenic rupture
  - if acute airway obstruction, give corticosteroids and consult ENT

# Palliative Care

## Principles and Quality of Life

- support, educate, and treat both patient and family
- address physical, psychological, social and spiritual needs
- focus on symptom management and comfort measures
- offer therapeutic environment and bereavement support
- ensure maintenance of human dignity

## End-of-Life Care Discussions

### When to Initiate End-of-Life Care Discussions
- recent hospitalization for serious illness
- severe progressive medical condition(s)
- death expected within 6-12 mo
- patient request
- medical aid in dying
  - important to discuss grief/bereavement with loved ones

## Power of Attorney

- see Ethical, Legal, and Organizational Medicine, ELOM10

## Instructional Advance Directives

- see Ethical, Legal, and Organizational Medicine, ELOM10

## Symptom Management

### Assessment Tools
- Edmonton Symptom Assessment System (ESAS): asks patients to rate intensity of 9 common cancer/palliative symptoms (pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being, shortness of breath, "other") and monitor over time
- Palliative Performance Scale (PPS): assesses 5 functional components (ambulation, activity and evidence of disease, self-care, intake, conscious level) to predict survival in terminally-ill patients
  - PPS scores are determined by reading from left to right at each PPS level until the level that best fits the patient's functional status is found
  - PPS <30% indicative of <3 mo prognosis



**Guidance on the Management of Pain in Older People**
Age Aging 2013; 42:1-57
The three most common sites of pain in older adults are the back, leg/knee and hip. Acetaminophen should be considered first-line treatment for the management of both acute and persistent pain, particularly that which is of musculoskeletal origin. NSAIDs should be prescribed with caution and co-prescribed with a PPI.

## Table 24. Palliative Performance Scale

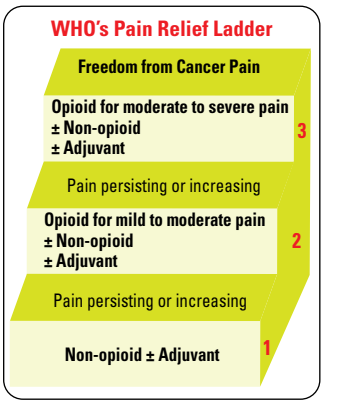
| PPS Level | Ambulation | Activity and Evidence of Disease | Self Care | Intake | Conscious Level |
|---|---|---|---|---|---|
| 100% | Full | Normal activity and work<br>No evidence of disease | Full | Normal | Full |
| 90% | Full | Normal activity and work<br>Some evidence of disease | Full | Normal | Full |
| 80% | Full | Normal activity with effor<br>Some evidence of disease | Full | Normal or reduced | Full |
| 70% | Reduced | Unable to do normal job/ work<br>Significant disease | Full | Normal or reduced | Full |
| 60% | Reduced | Unable to do hobby/ housework<br>Significant disease | Occasional assistance necessary | Normal or reduced | Full or confusion |
| 50% | Mainly sit/lie | Unable to do any work<br>Extensive disease | Occasional assistance necessary | Normal or reduced | Full or confusion |
| 40% | Mainly in bed | Unable to do most activities<br>Extensive disease | Mainly assisted | Normal or reduced | Full or drowsy ± confusion |
| 30% | Totally bed bound | Unable to do any activities<br>Extensive disease | Total care | Normal or reduced | Full or drowsy ± confusion |
| 20% | Totally bed bound | Unable to do any activities<br>Extensive disease | Total care | Minimal to sips | Full or drowsy ± confusion |
| 10% | Totally bed bound | Unable to do any activities<br>Extensive disease | Total care | Minimal to sips | Drowsy or coma ± confusion |
| 0% | Death | — | — | — | — |

Adapted from: Medical care of the dying, 4th ed. Victoria: Victoria Hospice Society, 2006. Version 2

## Table 25. Common Symptoms at the End of Life

| Symptom | Non-Pharmacologic Management | Pharmacologic Management |
|---|---|---|
| **Constipation** | Rule out obstruction, impaction, anorectal disease, spinal cord pathology; hydration; high fibre intake; increase mobility; medication review | Sennosides, lactulose, percutaneous endoscopic gastrostomy (PEG) |
| **Terminal Pulmonary Secretions ("Death Rattle")** | Oral suctioning, discontinue unnecessary IV solutions, oral hygiene, re-positioning (on side, elevated) | Scopolamine SC or transdermal<br>Hyoscine, Glycopurronium; monitor for adverse effects (xerostomia, delirium, sedation) |
| **Dyspnea** | Elevate head of bed, eliminate allergens, open window/ use fan | 1st line: opioids (e.g. morphine, hydromorphone);<br>Adjuncts: oxygen if hypoxemic, benzodiazepines if anxiety symptoms present, bronchodilators |
| **Hiccups** | Dry sugar, breathing in paper bag | Chlorpromazine, haloperidol, metoclopramide, baclofen, marijuana |
| **Nausea and Vomiting** | Frequent and small meals, avoid offensive strong odours, treat constipation if present | Raised intracranial pressure: dexamethasone<br>Anticipatory nausea, anxiety: lorazepam<br>Vestibular disease, vertigo: dimenhydrinate<br>Drug induced, hepatic or renal failure: prochlorperazine, haloperidol<br>GERD: PPI or H2 antagonist<br>Gastric stasis: metoclopramide<br>Bowel obstruction: metoclopramide, dexamethasone, octreotide |
| **Pain** | Hot and cold compresses, music therapy, relaxation techniques, individualized program of physical activity designed to improve flexibility, strength and endurance, and CBT | Nociceptive pain: non-opioids (NSAIDs, acetaminophen), weak opioids (codeine, hydrocodone, oxycodone), strong opioids (morphine, hydromorphone, oxycodone, fentanyl)<br>Neuropathic pain: anticonvulsants (gabapentin, pregabalin), antidepressants (TCAs, SSRIs), steroids (dexamethasone)<br>Bony pain: non-opioids, weak opioids, bisphosphonates, radiation therapy |
| **Pruritus** | Bathing with tepid water, avoid soap, bath oils; sodium bicarbonate for jaundice | Antihistamines, phenothiazines, topical corticosteroids, calamine lotion |
| **Fatigue** | Modify environment and activities to decrease energy expenditure, optimize fluid and electrolyte intake<br>Educate and support patient and family, exercise | Treat underlying condition if present |
| **Psychiatric** | CBT<br>Support groups<br>Art/Music Therapy | Agitation: antipsychotics<br>Confusion/Delirium: treat underlying etiology<br>Depression: Standard SSRIs, SNRIs may be too slow depending on patient prognosis, consider psychostimulants (e.g. methyphenidate, ketamine)<br>Treat underlying condition if present |

Source: J Am Geriatr Soc 2002;50:S205-S224, Am Fam Physician 2009;79(12):1059-1065, and N Engl J Med 2015; 373: 2549-2561




**Terminal Respiratory Secretions ("Death Rattle")**
Noise caused by the oscillatory movement of mucous secretions in the upper airway with inspiration and expiration

Serum creatinine does not reflect creatinine clearance in the elderly

Instead, use:
CrCl = (weight in kg)(140 – age)(1.23)
(mL/min) (serum creatinine in μmol/L)

Multiply by 0.85 for females

Limitations:
- Underestimates CrCl in patients without significant age-related decline in renal function
- Overestimates CrCl in patients with muscle mass reduced beyond normal aging

**Approach to Medication Review in the Elderly**
Ask patient to bring all their current medications
- Review Beer's Criteria (2015) to identify potentially inappropriate medications
- Screen for adverse drug effects and drug interactions
- Eliminate unnecessary (duplicate therapies or pharmacologic effects) medications
- Simplify dosing regimen where possible
- Discuss patient's goals of care to guide pharmacologic management of symptoms/disease

# Complementary and Alternative Medicine

## Epidemiology

- 50-75% of Canadians report some use of CAM over their lifetime, and only half will disclose this use to their physician
- use is highest in Western provinces and lowest in Atlantic provinces
- more likely to be used by younger patients and those with higher education and income
- examples: chiropractic, acupuncture, massage, naturopathy, homeopathy, traditional Chinese medicine, craniosacral therapy, osteopathy

**Most Common Uses of CAM**

- Back/neck problems
- Gynecological problems
- Anxiety
- Headaches
- Digestive problems
- Chronic fatigue syndromes

## Herbal Products

- over 50% of Canadians use natural health products (NHPs)
- most commonly used include echinacea, ginseng, ginkgo, garlic, St. John's wort, and soy
- relatively few herbal products have been shown to be effective in clinical trials
- many patients believe herbal products are inherently safe and are unaware of potential side effects and interactions with conventional medicines
- all NHPs must be regulated under The Natural Health Products Regulations as of January 1, 2004, including herbal remedies, homeopathic medicines, vitamins, minerals, traditional medicines, probiotics, amino acids, and essential fatty acids (e.g. omega-3)
- always ask patients whether they are taking any herbal product, herbal supplement, or other natural remedy. Further questions may include:
  - Are you taking any prescription or non-prescription medications for the same purpose as the herbal product?
  - Are you allergic to any plant products?
  - Are you pregnant or breastfeeding?
- information resources: National Centre for CAM (www.nccam.nih.gov), Health Canada website

**Table 26. Common Herbal Products**

| Common Name | Reported Uses | Possible Adverse Effects | Possible Drug Interactions |
|---|---|---|---|
| **Black Cohosh** | Menopausal symptoms, PMS, labour induction, arthritis | Hepatitis, liver failure, headaches, GI discomfort, heaviness in legs, weight problems | None reported |
| **Chamomile** | Mild sedative, anxiolytic, GI complaints, common cold | Allergic/contact dermatitis, anaphylaxis | Anxiolytics, sedatives |
| **Echinacea** | Common cold, flu, wound treatment, UTI, cancer | Hypersensitivity, hepatotoxicity with prolonged use, avoid use if immunosuppressed | Potentiates warfarin |
| **Evening Primrose** | Dysmenorrhea, menopausal Sx, inflammation, allergies, eczema, arthritis, MS | Headache, restlessness, nausea, diarrhea, may decrease seizure threshold | Anticoagulants, antiplatelets |
| **Feverfew** | Migraine prevention, RA, anti-inflammatory | Anxiety, upset stomach, skin rash, miscarriage | Anticoagulants, antiplatelets |
| **Flaxseed Oil** | Laxative, menopausal symptoms, source of omega-3 fatty acids | Diarrhea | Do not take with other medications as fibre content can bind drugs |
| **Garlic** | Elevated lipids, HTN, hyperglycemia, antimicrobial | GI irritation, contact dermatitis, may increase post-operative bleeding | Anticoagulants, potentiates antihypertensives |
| **Ginger** | Nausea, motion sickness, dyspepsia, anti-inflammatory | Heartburn, not to be used for morning sickness | None known |
| **Ginkgo Biloba** | Increases peripheral circulation (Alzheimer's disease, dementia, intermittent claudication), premenstrual syndrome, vertigo | Headache, cramping, bleeding, mild digestive problems; reports of intracranial hemorrhage | Anticoagulants, thiazide diuretics, MAO inhibitors |
| **Ginseng** | Energy enhancer, decreases stress, adjunct support for chemotherapy/ radiation | HTN, nervousness,insomnia, breakthrough bleeding, palpitations | Stimulant medications, antihypertensives, hormonal therapies |
| **Glucosamine** (Chondroitin) | Osteoarthritis | GI distress, headache, drowsiness, palpitations | Caution if shellfish allergy |
| **Saw Palmetto** | BPH, adjunct to finasteride | Mild GI distress | α-adrenergics, finasteride |
| **St. John's Wort** | Mild to moderate depression | Photosensitivity, increased liver enzymes, drowsiness, dizziness, nausea, headache | CNS depressants, contraindicated with indinavir |
| **Valerian Root** | Sedative, anxiolytic, muscle relaxant, PMS | Drowsiness, headache, digestive problems, paradoxical insomnia | CNS depressants, antihistamines |

Zink T, Chaffin J. Herbal "health"products: What family physicians need to know. *American Family Physician* 1998;58:1133-1140; NIH National Centre for Complementary and Alternative Medicine website (http://nccam.nih.gov/)

# Primary Care Models

**Table 27. Primary Care Models (Adapted from www.healthforceontario.ca)**

| | Characteristics |
|---|---|
| **Comprehensive Care Model** | FPs/GPs in solo practice with limited after-hours availability<br>Payment model: fee-for-service |
| **Family Health Team** | Groups of health care professionals (e.g. FPs, GPs, RNs, NPs, dieticians, social workers)<br>Wider range of services (e.g. rehabilitation, palliative care), with increased after-hours availability<br>Receives provincial funding for allied health<br>Patient enrolment is strongly encouraged<br>Payment model: blended capitation model i.e. age- and sex-adjusted base rate remuneration plus bonuses and incentives |
| **Family Health Group** | Group of ≥3 FPs, can utilize nurse-staffed, telephone health advisory services to provide around the clock primary care coverage<br>Physicians commit to enroll patients<br>Payment model: blended capitation model i.e. age- and sex-adjusted base rate remuneration plus bonuses and incentives |
| **Family Health Network** | Group of ≥3 FPs, can utilize NPs, with telephone health advisory services to provide around the clock primary care coverage<br>Payment model: salary-based |
| **Family Health Organization** | Same as FHT but usually larger in scale in terms of personnel<br>Physicians commit to enroll patients<br>Must sign governance and Family Health Organization agreements to join<br>Payment model: blended capitation model i.e. age- and sex-adjusted base rate remuneration plus bonuses and incentives |

FP = family physician; GP = general practitioner; RN = registered nurse; NP = nurse practitioner; FHT = family health teadm

# Antimicrobial Quick Reference

| Condition | Microorganisms | Antimicrobial |
|---|---|---|
| **RESPIRATORY/ENT** | | |
| **Acute Rhinitis** (common cold) | Rhinovirus, coronavirus, influenza, RSV, parainflunenza, adenovirus | None |
| **Pharyngitis** (sore throat) | Rhinovirus, adenovirus, influenza, parainfluenza, coxsackie virus, coronavirus | None |
| **Strep Pharyngitis** | Group A β-Hemolytic *Streptococcus* | *Children:*<br>1st line: penicillin V 40 mg/kg/d PO div bid-tid (max 750 mg/d) x 10 d (use adult dose if >27 kg)<br>amoxicillin 40 mg/kg/d PO div bid-tid x 10 d<br>2nd line: erythromycin estolate 40 mg/kg/d PO div bid-tid x 10 d<br>3rd line: cephalexin 25-50 mg/kg/d PO div qid x 10 d<br>cefprozil 15 mg/kg/d PO div bid x 10 d<br>*Adults:*<br>1st line: penicillin V 300 mg PO tid or 600 mg bid x 10 d<br>2nd line: erythromycin 250 mg PO qid x 10 d<br>3rd line: cephalexin 250 mg PO qid x 10 d<br>cefadroxil 500 mg PO bid x 10 d |
| **Sinusitis** | *S. pneumoniae*<br>*H. influenzae*<br>*M. catarrhalis*<br>*S. aureus* | *Children:*<br>1st line: amoxicillin 80 mg/kg/d PO div bid-tid x 5-10 d (max 3 g/d) x 10-14 d<br>2nd line: amoxicillin/clavulanate 40-80 mg/kg/d div bid (max 3 g/d) x 10-14 d<br>cefprozil 30 mg/kg/d PO div bid x 10-14 d<br>3rd line: cefuroxime-AX 30-40 mg/kg/d PO div bid x 10-14 d<br>clarithromycin 15 mg/kg/d PO div bid x 10-14 d<br>*Adults:*<br>1st line: amoxicillin 500 mg PO tid x 5-10 d<br>2nd line: amoxicillin/clavulanate 500 or 875 mg PO bid x 5-10 d<br>cefuroxime-AX 250-500 mg PO bid x 5-10 d<br>3rd line: levofloxacin 500 mg PO OD x 5-10 d<br>moxifloxacin 400 mg PO OD x 5-10 d |
| **RESPIRATORY/ENT** | | |
| **Acute Otitis Media** | *S. pneumoniae*<br>*H. influenzae*<br>*M. catarrhalis*<br>Group A *Strep*<br>*S. aureus* | *Children:*<br>Treat if under age 6 mo<br>If age 6-24 mo, watchful waiting appropriate if parents can observe child for 48-72 h with appropriate medical follow-up<br>If age >24 mo, treat if worsens after 48-72 h<br>10 d course if age <24 mo, 5 d course if age >24 mo<br>1st line: amoxicillin 80 mg/kg/d PO div bid-tid (max 3 g/d)<br>2nd line: amoxicillin/clavulanate 40-80 mg/kg/d PO div bid (max 3 g/d)<br>cefprozil 30 mg/kg/d PO div bid<br>3rd line: cefuroxime-AX 30-40 mg/kg/d PO div bid<br>clarithromycin 15 mg/kg/d PO div bid<br>Chronic TM perforation or ventilation tubes: Ciprodex® otic suspension 4 drops bid x 5 d<br>*Adults:*<br>1st line: amoxicillin 500 mg PO tid x 7-10 d<br>2nd line: amoxicillin/clavulanate 500 mg PO tid or 875 mg PO bid x 7-10 d<br>cefprozil 250-500 mg PO bid x 7-10 d<br>Chronic TM perforation or ventilation tubes: Ciprodex® otic suspension 4 drops bid x 5 d |
| **Otitis Externa** | *P. aeruginosa*<br>Coliforms<br>*S. aureus* | Cortisporin® otic solution 4 drops tid or qid (3 drops tid or qid for children)<br>TM defect: Ciprodex® otic suspension 4 drops bid x 5 d<br>Necrotizing (i.e. bone involvement): ciprofloxacin 750 mg PO bid x 4-8 wk |
| **Bronchitis** | *H. influenzae*, parainfluenza, coronavirus, rhinovirus, RSV | None |
| **Community Acquired Pneumonia: Outpatient without Comorbidity** | *S. pneumoniae*<br>*M. pneumoniae*<br>*C. pneumoniae* | 1st line: amoxicillin 1000 mg PO tid x 7-14 d<br>(for patients over age 50 where mycoplasma infection is less likely)<br>erythromycin 500 mg PO qid x 7-14 d<br>clarithromycin 500 mg PO bid or 1000 mg (ER) PO OD x 7-14 d<br>azithromycin 500 mg PO on 1st d then 250 mg PO OD x 4 d or 500 mg PO OD x 3 d<br>2nd line: doxycycline 100 mg PO on 1st d then 100 mg PO OD x 7-14 d |
| **Community Acquired Pneumonia: Outpatient with Comorbidity** | *S. pneumoniae*<br>*M. pneumoniae*<br>*C. pneumoniae*<br>*H. influenzae* | **ANYONE of the β-lactam agents below:**<br>amoxicillin 1000 mg PO tid x 7-14 d<br>amoxicillin/clavulanate 500 mg PO tid or 875 mg PO bid x 7-14 d<br>cefuroxime-AX 500 mg PO bid x 7-14 d<br>cefprozil 500 mg PO bid x 7-14 d<br>**PLUS ONE of the following:**<br>clarithromycin 500 mg PO bid or 1000 mg (ER) PO OD x 7-14 d<br>azithromycin 500 mg PO OD on 1st d then 250 mg PO OD x 4 d<br>doxycycline 100 mg PO bid on 1st d then 100 mg PO OD x 7-14 d<br>**OR ANY ONE of the following:**<br>levofloxacin 750 mg PO OD x 7-14 d<br>moxifloxacin 400 mg PO OD x 7-14 d |
| **Dental Infections/Periapical and Periodontal Abscesses** | Oral Flora | penicillin V potassium 500 mg PO qid x 7-10 d<br>clindamycin 300 mg PO qid or 600 mg bid x 7-10 d |

| Condition | Microorganisms | Antimicrobial |
|---|---|---|
| **GASTROENTEROLOGY** | | |
| **Diarrhea – Enteritis** | Enterotoxigenic *E. coli* (ETEC)<br>*Campylobacter*<br>*Salmonella*<br>*Shigella*<br>Viruses<br>Protozoa | Mild to moderate (i.e. <3 bowel movements per day, no blood, no fever): OTC loperamide 4 mg PO STAT then 2 mg PO after each loose stool (max 8 doses/d)<br>OTC bismuth subsalicylate (Pepto Bismol®) 2 tabs or 30 mL repeat q30min prn (max 8 doses/d)<br>(prevention: 2 tabs or 30 mL qid with meals and in the evening)<br><br>Moderate to severe (i.e. >3 BM/d, blood, fever):<br>olfloxacin 400 mg PO single dose or 300 mg PO bid x 3 d (prevention: 300 mg PO OD)<br>norfloxacin 800 mg PO single dose or 400 mg PO bid x 1-3 d (prevention: 400 mg PO OD)<br>ciprofloxacin 750 mg PO single dose or 500 mg PO bid x 1-3 d (prevention: 500 mg PO OD)<br>levofloxacin 500 mg PO OD x 1-3 d (prevention: 500 mg PO OD)<br>azithromycin 1000 mg PO single dose or 500 mg PO OD x 1-3 d (children: 10 mg/kg/d x 3 d)<br><br>*Azithromycin:*<br>Recommended primarily for Thailand, India, Nepal, and Indonesia where *Campylobacter* resistance to quinolones is high<br>Considered drug of choice for children because of safety, tolerability, and ease of administration |
| **Diarrhea – Post Antibiotics** (common with clindamycin) | *C. difficile* | Mild to moderate (WBC <5 x $10^9$/L and Cr <1.5 x baseline): metronidazole 500 mg PO tid or 250 mg PO qid x 10 d (children: 15-30 mg/kg/d PO div tid-qid max 4 g/d)<br><br>Severe (WBC ≥15 x $10^9$/L and Cr ≥1.5 x baseline):<br>vancomycin 125 mg PO qid x 10-14 d (children: 40 mg/kg/d PO div tid-qid x 10-14 d max 2 g/d) |
| **Peptic Ulcer Disease** (non-NSAID related) | *H. pylori* | 1st line: (PPI PO bid + amoxicillin 1000 mg PO bid + clarithromycin 500 mg PO bid x 7 d<br>[e.g. HP-PAC: lansoprazole 30 mg PO bid + amoxicillin 1000 mg PO bid + clarithromycin 500 mg PO bid x 7 d])<br>(PPI PO bid + metronidazole 500 mg PO bid + clarithromycin 500 mg or 250 mg PO bid x 7 d)<br>2nd line: (PPI PO bid + metronidazole 500 mg PO bid + amoxicillin 1000 mg PO bid x 7 d)<br>(PPI PO bid + bismuth subsalicylate 2 tabs or 30 mL qid + metronidazole 250 mg PO qid + tetracycline 500 mg PO qid x 7-14 d)<br><br>PPI: lansoprazole 30 mg or omeprazole 20 mg or pantoprazole 40 mg or rabeprazole 20 mg |
| **DERMATOLOGIC** | | |
| **Head and Pubic Lice** (crabs) | *Pediculosis humanus capitis*<br>*Phthirus pubis* | permethrin cream 1%: apply as liquid onto washed hair for 10 min, then rinse; repeat in 1 wk |
| **Vulvovaginal Candidiasis** | *Candida* | Treat only if patient is symptomatic<br>fluconazole 150 mg PO single dose<br>miconazole 2% cream (Monistat 7®): one applicator (5 g) intravaginally qhs x 7 d<br>multiple other OTC azole treatments |
| **Bacterial Vaginosis** | Overgrowth of:<br>*G. vaginalis*<br>*M. hominis*<br>Anaerobes | If patient is asymptomatic, treatment is unnecessary unless high-risk pregnancy, prior IUD insertion, gynecologic surgery, induced abortion, or upper tract instrumentation<br>1st line: metronidazole 500 mg PO bid x 7 d<br>metronidazole 0.75% gel: one applicator (5 g) intravaginally qhs x 5 d<br>clindamycin 2% cream: one applicator (5 g) intravaginally qhs x 7 d<br>2nd line: metronidazole 2 g PO single dose<br>clindamycin 300 mg PO bid x 7 d |
| **Herpes** | Herpes simplex virus | 1° episode: acyclovir 400 mg PO tid x 5-7 d<br>famciclovir 250 mg PO tid x 5-7 d<br>valacyclovir 500-1000 mg PO bid x 5-7 d<br>Recurrent Episode: acyclovir 400 mg PO tid x 5 d or 800 mg PO bid x 5 d or 800 mg PO tid x 2 d<br>famciclovir 125 mg PO bid x 5 d<br>valacyclovir 500 mg PO bid x 3 d or 1000 mg PO OD x 3 d<br>Pregnancy:<br>1° episode: acyclovir 200 mg PO 5x/d x 5-10 d<br>Prior infection within previous yr: acyclovir 200 mg PO qid at 36 wk<br>valacyclovir 500 mg PO bid at 36 wk |
| **Gonorrhea/Chlamydia** | *N. gonorrhoeae*<br>*C. trachomatis* | ceftriaxone 250 mg IM x 1 dose + azithromycin 1 g PO<br>single dose or doxycycline 100 mg PO bid x 7 d |
| **Mastitis** | *S. aureus*<br>*S. pyogenes* | cloxacillin 500 mg PO qid x 7 d<br>cephalexin 500 mg PO qid x 7 d |
| **Tinea Cruris/Pedis** (jock itch/athlete's foot) | Trichophyton | clotrimazole 1% cream bid<br>ketoconazole 2% cream bid |
| **Uncomplicated Cellulitis** | *S. aureus*<br>Group A *Streptococcus* | *Children:*<br>1st line: cephalexin 50-100 mg/kg/d div qid x 10-14 d<br>2nd line: cloxacillin 50 mg/kg/d div qid x 10-14 d<br>clindamycin 25 mg/kg/d x 10-14 d<br>*Adults:*<br>1st line: cephalexin 500 mg PO qid x 10-14 d<br>2nd line: cloxacillin 500 mg PO qid x 10-14 d<br>clindamycin 300 mg PO x 10-14 d |

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# G Gastroenterology

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# Acronyms

| | |
|---|---|
| ALF | acute liver failure |
| BE | Barrett's esophagus |
| BT | biologic therapy |
| CCK | cholecystokinin |
| CD | Crohn's disease |
| CHF | congestive heart failure |
| CMV | cytomegalovirus |
| CNS | central nervous system |
| CXR | chest X-ray |
| DGP | deamidated gliadin peptides |
| DES | diffuse esophageal spasm |
| DM | diabetes mellitus |
| EBV | Epstein-Barr virus |
| EIM | extraintestinal manifestation |
| EN | enteral nutrition |
| EPEC | enteropathogenic *E. coli* |
| ERCP | endoscopic retrograde cholangiopancreatography |
| ETEC | enterotoxigenic *E. coli* |
| EUS | endoscopic ultrasound |
| EVL | endoscopic variceal ligation |
| GE | gastroesophageal |
| GERD | gastroesophageal reflux disease |
| GI | gastrointestinal |
| HAV | hepatitis A virus |
| HBV | hepatitis B virus |
| HCC | hepatocellular carcinoma |
| HCV | hepatitis C virus |
| HRS | hepatorenal syndrome |
| HSV | herpes simplex virus |
| HVPG | hepatic venous pressure gradient |
| IBD | inflammatory bowel disease |
| IBS | irritable bowel syndrome |
| ICP | intracranial pressure |
| INH | isoniazid |
| LES | lower esophageal sphincter |
| MRCP | magnetic resonance cholangiopancreatography |
| MS | multiple sclerosis |
| NAC | N-acetylcysteine |
| NAFLD | non-alcoholic fatty liver disease |
| NERD | non-erosive reflux disease |
| NMS | neuroleptic malignant syndrome |
| OGD | oesophagogastroduodenoscopy |
| PBC | primary biliary cirrhosis |
| PN | parenteral nutrition |
| PPI | proton pump inhibitor |
| PSC | primary sclerosing cholangitis |
| PTC | percutaneous transhepatic cholangiography |
| PUD | peptic ulcer disease |
| RA | rheumatoid arthritis |
| SBP | spontaneous bacterial peritonitis |
| TB | tuberculosis |
| TIPS | transjugular intrahepatic portosystemic shunt |
| TNF | tumour necrosis factor |
| TPN | total parenteral nutrition |
| TTG | tissue transglutaminase |
| UC | ulcerative colitis |
| UGIB | upper gastrointestinal bleed |

# Anatomy Review

## Overview of Gastrointestinal Tract

- the gastrointestinal tract runs from mouth to anus ("gum to bum")

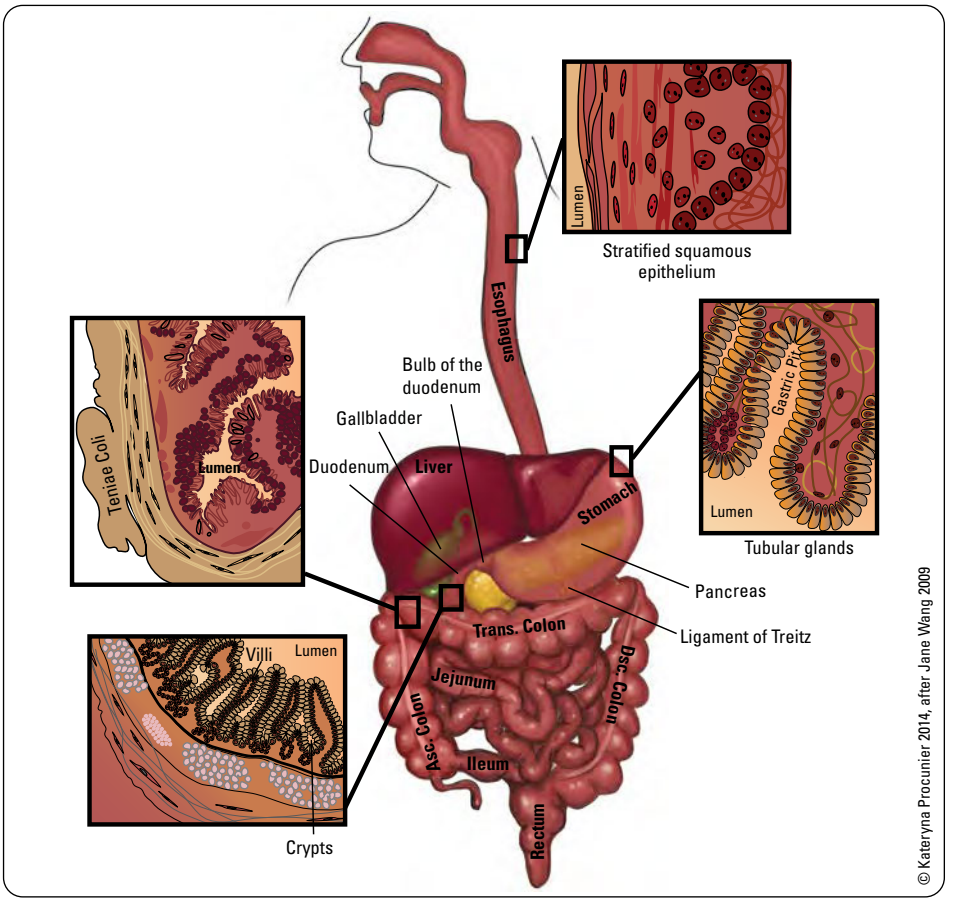



**Figure 1. Overview of gastrointestinal tract**

**Table 1. Summary of Gastrointestinal Tract Structure and Function**

| Organ | Function | Blood Supply | Innervation | Histology and Structural Features |
|---|---|---|---|---|
| **Esophagus** | Muscular tube approximately 40 cm long with a diameter of 2 cm<br>Extends from pharynx to the stomach | Arterial: left gastric artery and left inferior phrenic artery<br>Venous:<br>Left gastric vein → portal venous system<br>Esophageal veins → azygos vein → IVC (systemic) | Parasympathetic innervation via anterior and posterior gastric nerves (vagal trunks)<br>Sympathetic innervation via thoracic trunks of the greater splanchnic nerves | Mucosa: stratified squamous epithelium<br>Submucosa: connective tissue, lymphocytes, plasma cells, nerve cells<br>Muscularis propria (muscularis externa): inner circular, outer longitudinal muscle<br>Upper 1/3: striated muscle<br>Middle 1/3: transition zone<br>Lower 1/3: smooth muscle |
| **Stomach** | Delivers food to intestine for digestion and absorption<br>Secretes acid, probably to reduce enteric infections/pneumonia; facilitate digestion of protein and absorption of iron/B12<br>Secretes intrinsic factor to facilitate B12 absorption<br>Minor contribution to initial protein digestion via pepsin | Lesser curvature<br>Right and left gastric arteries (from celiac trunk)<br>Greater curvature<br>Right and left gastro-omental (gastroepiploic) arteries (from gastroduodenal and splenic arteries respectively)<br>Fundus: short and posterior gastric arteries (from the splenic artery) | Parasympathetic innervation via vagus nerve<br>Sympathetic innervation via celiac plexus (from T6-T9) | 5 parts<br>Cardia<br>Fundus<br>Body<br>Antrum<br>Pylorus |
| **Duodenum** | Modulates enteral pH via secretin → decreased gastric acid secretion, increased bicarbonate secretion<br>Secretes CCK to stimulate gallbladder contraction<br>Site of iron absorption | Branches of celiac artery and superior mesenteric artery | Parasympathetic innervation via vagus nerve<br>Sympathetic innervation via greater and lesser splanchnic nerves | 4 parts<br>Superior (5 cm)<br>Descending (7-10 cm)<br>Horizontal (6-8 cm)<br>Ascending (5 cm)<br>1st part is intraperitoneal; rest is retroperitoneal |
| **Jejunum** | Absorption of sodium, water, and nutrients (protein, carbohydrates, fat, folic acid, and vitamin A, B, C, D, E, K) | Superior mesenteric artery | Parasympathetic innervation via fibres of the posterior vagal trunk<br>Sympathetic innervation via fibres of T8-T10 | Deep red colour<br>2-4 cm in thickness<br>Thick and heavy wall<br>Plicae circulares are large, tall, and closely packed<br>Has long vasa recta<br>Scant fat in mesentery<br>Scant Peyer's patches |
| **Ileum** | Absorption of sodium, water, nutrients, soluble vitamins (only site of vitamin B12 absorption), and bile salts (entero-hepatic circulation) | Superior mesenteric artery | Same as jejunum | When compared to jejunum<br>Paler pink colour<br>2-3 cm in thickness<br>Thin and light walls<br>Plicae circulares are small and sparse<br>Contains more mesenteric fat<br>Many Peyer's patches |
| **Large Bowel** | Absorption of water (5-10% of total water)<br>Bacteria: further digestion of chyme and metabolism of undigested CHO to short chain fatty acids<br>Formation and storage of feces | Branches of superior and inferior mesenteric arteries<br>Rectal blood supply: sigmoid, right pudendal, and rectal arteries | Parasympathetic innervation via vagus nerve<br>Sympathetic innervation via greater and lesser splanchnic nerves | Consists of cecum, colon (ascending, transverse, descending, and sigmoid), rectum and anal canal<br>Features include teniae coli, haustra, and omental appendices |
| **Liver** | Glucose homeostasis<br>Plasma protein synthesis<br>Lipid and lipoprotein synthesis<br>Bile acid synthesis and secretion<br>Vitamin A, D, E, K, B12 storage<br>Biotransformation, detoxification<br>Excretion of compounds | 2 sources<br>Portal vein (75-80%)<br>Hepatic artery (20-25%) | Parasympathetic innervation via fibres of the anterior and posterior vagal trunks<br>Sympathetic innervation via fibres of the celiac plexus | Largest internal organ<br>Composed of 4 lobes (left, right, caudate, quadrate), and divided into 8 segments |
| **Biliary Tract** | Gallbladder functions to store and release bile that is produced in the liver<br>Bile is used to emulsify fat and is composed of cholesterol, lecithin, bile acids, and bilirubin<br>CCK stimulates gallbladder emptying while trypsin and chymotrypsin inhibit bile release | Cystic artery | Parasympathetic innervation via vagus nerve<br>Sympathetic and visceral innervation via celiac nerve plexus<br>Somatic afferent fibres via right phrenic nerve | Consists of the hepatic ducts (intrahepatic, left, right and common), gallbladder, cystic duct, common bile duct, and ampulla of Vater |
| **Pancreas** | Endocrine function: islets of Langerhans produce glucagon, insulin, and somatostatin (from the α, β, and δ cells, respectively)<br>Exocrine function: digestive enzymes are produced including amylase, lipase, trypsin, chymotrypsin, and carboxypeptidase | Anterior superior pancreaticoduodenal artery (from the celiac trunk)<br>Anterior inferior pancreaticoduodenal artery (from the superior mesenteric artery)<br>Dorsal pancreatic artery (from the splenic artery)<br>Pancreatic veins drain into the portal, splenic, and superior mesenteric veins | Parasympathetic innervation via vagus nerve<br>Sympathetic innervation via abdominopelvic splanchnic nerves | 4 parts of pancreas: head (includes uncinate process), neck, body, and tail<br>(Major) pancreatic duct connecting to common bile duct prior to ampulla of Vater<br>Accessory pancreatic duct connected directly to duodenum |

# Visualizing the Gaastrointestinal Tract

- see Medical Imaging, MI16

### Esophagus, Stomach, Duodenum

- OGD: best visualization of mucosa; also allows for therapeutic intervention (e.g. banding varices, thermal therapy/clipping/injecting bleeding ulcers, and dilatation e.g. treatment of esophageal strictures)
  - consider barium swallow first if dysphagia, decreased level of consciousness (increases risk of aspiration), inability to cooperate (increases risk of pharyngeal trauma during intubation), possibility of fistulas
  - endotracheal intubation first if massive upper GI bleed, acidemia, or inability to protect airway

### Small Bowel

- most difficult to visualize, especially if mucosal detail is needed
- CT enterography more accurate than small bowel follow through, but both have low sensitivity
- MRI small bowel imaging increasingly available, especially useful if radiation exposure is an issue (e.g. young patient, multiple radiological images already done)
  - note: MRI enteroclysis: luminal contrast administered by nasojejunal tube to dilate the small bowel – disliked by both radiologist and patient, but may improve sensitivity
- "double balloon" enteroscopy (enteroscope with proximal and distal balloons to propel endoscope into jejunum from mouth or into jejunum/ileum or into ileum from anus) may be most sensitive but currently available only in selected centres; technically demanding
- wireless endoscopy capsule (26 x 11 mm capsule is swallowed, transmits images to a computer; contraindicated in bowel obstruction) is also accurate in diagnosis but unable to provide any therapeutic intervention

### Colon and Terminal Ileum

- colonoscopy, with biopsy if required; contraindicated in perforation, acute diverticulitis, and severe colitis (increased risk of perforation)
- CT colonography ("virtual colonoscopy") more accurate in diagnosing diverticulosis, extrinsic pressure on colon (e.g. ovarian cancer compressing sigmoid colon), and fistulae; increasing evidence for use in colorectal cancer screening, especially for assessment of right side of colon in cases where colonoscopy is less sensitive
  - most often used when optical endoscopic colonoscopy is a risk (e.g. frail elderly) or unsuccessful (e.g. stricture)

### Pancreatic/Biliary Duct

- MRCP almost as sensitive as ERCP in determining if bile duct obstruction present, but less accurate in determining cause of obstruction (tumour, stone, stricture)
- ERCP if therapeutic intervention likely to be required: strong suspicion of stone, obstruction requiring stenting, or if tissue sampling required
- Endoscopic ultrasound can provide detailed anatomy of biliary tree and pancreas with potential for sampling/intervention (cyst drainage)

**Acute Upper Abdominal Pain**
Remember to rule out thoracic sources, e.g. myocardial infarction, pneumonia, dissecting aneurysm

# Differential Diagnosis of Common Complaints

- see General Surgery, GS4

**Table 2. Differential Diagnosis of Common Presenting Complaints**

| CHRONIC/ RECURRENT ABDOMINAL PAIN | Inflammatory | Neoplastic/ Vascular | Toxin | Other |
|---|---|---|---|---|
| | PUD<br>Biliary colic<br>IBD<br>Chronic pancreatitis | Recurrent bowel obstruction<br>Mesenteric ischemia<br>Sickle cell anemia | Lead poisoning | Mittleschmertz<br>Endometriosis<br>Porphyria<br>IBS<br>Radiculopathy<br>Abdominal wall pain syndrome |
| **ACUTE DIARRHEA** | **Inflammatory** | | **Non-Inflammatory** | |
| *Causes of bloody diarrhea | **Bacterial**<br>*Shigella**<br>*Salmonella**<br>*Campylobacter**<br>*Yersinia**<br>*E. coli* (EHEC 0157:H7)* | **Protozoal**<br>*E. histolytica** (amoebiasis)<br>*Strongyloides*<br><br>**Others**<br>NSAIDs<br>IBD*<br>Ischemic* | **Bacterial**<br>*S. aureus*<br>*C. perfringens*<br>*B. cereus*<br>*E. coli* (enterotoxigenic, enteropathogenic )<br>*Salmonella enteritidis*<br>*Vibrio cholera*<br>**Protozoal**<br>*Giardia lamblia* | **Viral**<br>Rotavirus<br>Norwalk<br>CMV<br>**Drugs**<br>Antibiotics<br>Colchicine<br>Laxatives<br>Antacids (magnesium) |

**Obscure But Treatable Causes of Abdominal Pain**
- Acute Intermittent Porphyria
- Hereditary Angioedema
- Familial Mediterranean Fever
- Vasculitis (e.g. polyarteritis nodosa)

**Inflammatory Diarrhea**: Occurs when there is damage to the mucosal lining or brush border, which leads to a passive loss of protein-rich fluids and a decreased ability to absorb these lost fluids. Diarrhea may be profuse or very small in volume. Often associated with abdominal pain ± fever and chills
**Non-Inflammatory Diarrhea**: No damage to the mucosal lining. Nausea/vomiting may be present. Fever, chills, blood in the stool, severe abdominal pain or tenderness are not present

**Table 2. Differential Diagnosis of Common Presenting Complaints** (continued)

| **CHRONIC DIARRHEA** | **Organic** | | | | **Functional** |
|---|---|---|---|---|---|
| *Causes of bloody diarrhea | **Inflammatory** | **Secretory** | **Steatorrhea** | **Osmotic** | |
| | IBD*<br>Infectious (TB, CMV, HSV)<br>Ischemic bowel*<br>Radiation colitis<br>Neoplasia<br><br>*C. difficile* rarely causes bleeding | Stimulant laxatives<br>Post-ileal resection/ cholecystectomy (bile salts)<br>Bacterial toxins<br>Vasculitis<br>Neoplasia* (colon ca, carcinoid, VIPoma)<br>Addison's disease<br>Congenital syndromes | *Giardia lamblia*<br>Celiac sprue<br>Chronic pancreatitis<br>Chronic cholestasis | Osmotic laxatives<br>Lactose intolerance<br>Chewing gum (sorbitol, mannitol) | IBS<br>Constipation (overflow diarrhea)<br>Anal sphincter dysfunction |
| **CONSTIPATION: if no associated rectal bleeding/weight loss, etc., usually no cause found (and dysmotility assumed)** | | | | | |
| | Colorectal cancer<br>Stricture<br>Extrinsic compression<br>Anal disease<br>Rectocele | Medications (narcotics, antidepressants, calcium channel blockers)<br>Metabolic (DM, thyroid, hypercalcemia) | Neurologic (Parkinson's, MS, stroke)<br>Collagen vascular disease (scleroderma, dermatomyositis) | | |
| **NAUSEA/VOMITING** | **With Abdominal Pain** | | **Without Abdominal Pain** | | |
| | **Relieved by Vomiting** | **Not Relieved by Vomiting** | **Headache/Dizziness** | **No Other Symptoms** | |
| | Gastric outlet obstruction<br>Small bowel obstruction<br>GERD (regurgitation more common) | Gallbladder disease<br>Pancreatitis<br>Myocardial infarction<br>Hepatitis<br>Infectious Gastroenteritis | Cerebral tumour<br>Migraine<br>Vestibular disease<br>Increased ICP | Drugs<br>Uremia<br>Pregnancy<br>Metabolic (e.g. hypercalcemia)<br>Gastroparesis (e.g. DM)<br>Ketoacidosis | |
| **DYSPEPSIA** | **Common** | | **Uncommon** | **Rare** | |
| | Functional dyspepsia<br>Drug side effect<br>Peptic ulcer<br>GERD (esophagitis) | | Angina<br>Crohn's disease<br>Cancer (stomach, pancreas, liver)<br>Gallstones<br>Aerophagia | Giardia lamblia<br>Malabsorption (celiac sprue)<br>Pancreatitis | |
| **UPPER GI BLEED** | **Common** | | **Uncommon** | **Rare** | |
| | Ulcers (*H. pylori*, ASA, NSAIDs)<br>Esophageal varices<br>Mallory-Weiss tears<br>Erosive esophagitis<br>Erosive gastritis | | Tumours<br>Arteriovenous malformation<br>Dieulafoy's lesion (arterial)<br>Gastric antral vascular ectasia (GAVE)<br>Portal hypertensive gastropathy | Aorto-enteric fistulas<br>Hemobilia | |
| **LOWER GI BLEED** | **Common** | | **Uncommon** | **Rare** | |
| | Diverticulosis<br>Ischemia<br>Angiodysplasia (elderly)<br>Infectious<br>Anorectal (hemorrhoids, fissure, ulcer) | | Upper GI bleed (brisk)<br>Post-polypectomy<br>Radiation colitis<br>IBD | Intussusception<br>Vasculitides<br>Stercoral ulcer<br>Coagulopathies | |
| **DYSPHAGIA** | **Mechanical (Solids)** | | **Motility (Solids and Liquids)** | **Other** | |
| | Peptic stricture/cancer<br>Eosinophilic esophagitis<br>Extrinsic compression<br>Schatzki ring/esophageal web<br>Zenker's diverticulum | | Achalasia<br>Diffuse esophageal spasm<br>Scleroderma | Foreign body<br>Eosinophilic esophagitis | |
| **ODYNOPHAGIA** | **Infection** | **Inflammation/Ulceration** | **Drugs** | **Other** | |
| | Candida<br>Herpes<br>CMV (common in those who are immunosuppressed) | Caustic damage<br>Eosinophilic esophagitis | Quinidine<br>Iron<br>Vitamin C<br>Antibiotics (e.g. tetracycline)<br>Bisphosphonates | Radiation | |
| **ABDOMINAL DISTENTION** | **Fluid (Ascites)** | **Flatulence** | **Feces** | **Other** | |
| | **Portal HTN** / **Normal Portal Pressure** | | | | |
| | Cirrhosis<br>Cardiac failure<br>Hepatic vein thrombosis<br>/<br>Cancer (especially ovarian)<br>Pancreatitis<br>TB | Functional bowel disease (e.g. IBS)<br>Fibre<br>Lactose intolerance<br>Chewing gum (e.g. sorbitol, mannitol) | Constipation<br>Colonic obstruction<br>Dysmotility | Pregnancy (fetus)<br>Obesity (fat)<br>Blood<br>Large tumours (fatal growth) | |



IBD Is a common cause of bloody diarrhea but can be diagnosed only if mimickers are excluded. Chiefly, infection, ischemia and medication side-effects



**Commonly Forgotten Causes of Vomiting**

- Drugs
- Uremia
- CNS Disease
- Pregnancy
- Marijuana (cannabinoid hyperemesis)



**Difference Between Dysphagia and Odynophagia**

- **Dysphagia**: Difficulty swallowing due to mechanical obstruction or dysmotility of the esophagus or pharynx
- **Odynophagia**: Pain when swallowing due to ulceration or inflammation (e.g. eosinophilic esophagitis) in the esophagus pharynx



**Differential Diagnosis of Abdominal Distention**

**6 Fs**
**F**at
**F**eces
**F**etus
**F**latus
**F**luid
**F**atal Growth

**Table 2. Differential Diagnosis of Common Presenting Complaints** (continued)

| | | | |
|---|---|---|---|
| **JAUNDICE (UNCONJUGATED BILIRUBIN)** | **Overproduction** | **Decreased Hepatic Intake** | **Decreased Conjugation** |
| | Hemolysis<br>Ineffective erythropoiesis (e.g. megaloblastic anemias) | Gilbert's syndrome<br>Drugs (e.g. rifampin) | Drug inhibition (e.g. chloramphenicol)<br>Crigler-Najjar syndromes type I and II<br>Gilbert's syndrome<br>Neonatal jaundice |
| **JAUNDICE (CONJUGATED BILIRUBIN)** | **Common** | | **Uncommon** |
| | Hepatocellular disease<br>Drugs<br>Cirrhosis (any cause)<br>Inflammation (hepatitis, any cause)<br>Infiltrative (e.g. hemochromatosis)<br>Familial disorders (e.g. Rotor syndrome, Dubin-Johnson syndrome, cholestasis of pregnancy)<br>PBC<br>PSC<br>Sepsis<br>Post-operative/TPN | | **Intraductal obstruction**<br>Gallstones<br>Biliary stricture<br>Parasites<br>Malignancy (cholangiocarcinoma)<br>Sclerosing cholangitis<br>**Extraductal obstruction**<br>Malignancy (e.g. pancreatic cancer, lymphoma)<br>Metastases in peri-portal nodes<br>**Inflammation (e.g. pancreatitis)** |

**Bowel Ischemia**
The splenic flexure and rectosigmoid junction are watershed areas and are susceptible to ischemia. History and symptoms include acute onset crampy left abdominal pain, absence of abdominal tenderness on exam, rectal bleeding, and risk factors for embolization, atherosclerosis and atrial fibrillation

# Esophagus

## Gastroesophageal Reflux Disease

### Definition
- a condition which develops when the reflux of gastric content causes troublesome symptoms or complications

### Etiology
- inappropriate transient relaxations of LES – most common cause
- low basal LES tone (especially in scleroderma)
- contributing factors include: delayed esophageal clearance, delayed gastric emptying, obesity, pregnancy, acid hypersecretion (rare) from Zollinger-Ellison syndrome (gastrin-secreting tumour)
- hiatus hernia worsens reflux, does not cause it (see General Surgery, GS13)

### Clinical Features
- "heartburn" (pyrosis) and regurgitation (together are 80% sensitive and specific for reflux); less sensitive and less specific: water brash, sensation of a lump in the throat (globus sensation), and frequent belching
  - non-esophageal symptoms are increasingly recognized of being poor predictors of reflux

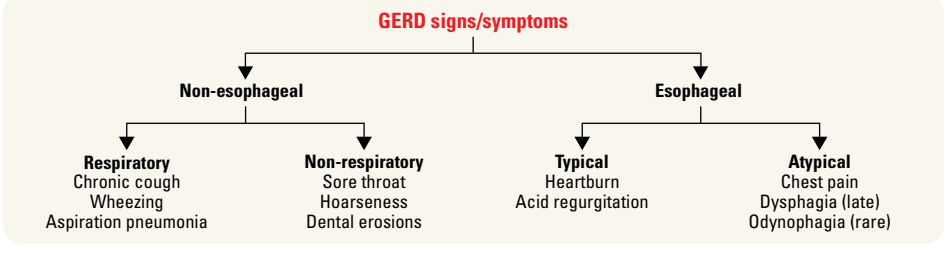



**Figure 2. Signs and symptoms of GERD**

**Dyspepsia** = postprandial fullness, early satiety, epigastric pain, or burning

**Foods/Substances that may aggravate GERD Symptoms (but diet does not change the underlying disease)**
- EtOH
- Caffeine
- Tobacco
- Fatty/fried foods
- Chocolate
- Peppermint
- Spicy foods
- Citrus fruit juices

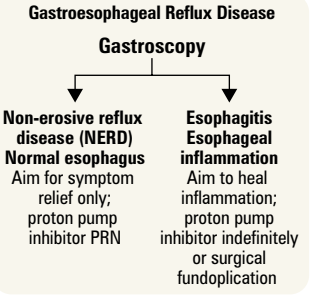



**Figure 3. Classification and gastroscopic findings of GERD**

### Investigations
- usually, a clinical diagnosis is sufficient based on symptom history and relief following a trial of pharmacotherapy (PPI: symptom relief 80% sensitive for reflux)
- however, response to anti-secretory agents such as PPI is not a requirement for GERD diagnosis
- gastroscopy indications (Ann Intern Med 2012;157:808-816)
  - absolute indications
    - heartburn accompanied by red-flags (bleeding, weight loss, dysphagia, persisting vomiting, family history of GI cancer etc.)
    - persistent reflux symptoms or prior severe erosive esophagitis after therapeutic trial of 4-8 wk of PPI 2x daily
    - history suggests esophageal stricture especially dysphagia
    - high risk for Barrett's (male, age >50, obese, white, tobacco use, long history of symptoms)
- repeat endoscopy after 6-8 wk of PPI therapy indicated if: severe esophagitis because it can mask Barrett's esophagus or symptoms

- esophageal manometry (study of esophageal motility): indicated in patients who have a normal gastroscopy but with chest pain and/or dysphagia
  - done to diagnose abnormal peristalsis and/or decreased LES tone, but cannot detect presence of reflux; indicated before surgical fundoplication to ensure intact esophageal function; exclude alternative diagnoses like scleroderma and achalasia
  - surgical fundoplication (wrapping of gastric fundus around the lower end of the esophagus) more likely to alleviate symptoms if lower esophageal pressure is diminished; less likely to be successful if abnormal peristalsis
- 24 h pH monitoring: most accurate test for reflux, but not required or performed in most cases
  - most useful if PPIs do not improve symptoms

### Treatment
- PPIs are the most effective therapy and usually need to be continued as maintenance therapy
- on-demand: antacids ($Mg(OH)_2$, $Al(OH)_3$, alginate), H2-blockers, or PPIs can be used for NERD
- diet helps symptoms, not the disease; avoid alcohol, coffee, spices, tomatoes, and citrus juices
- only beneficial lifestyle changes are weight loss (if obese) and elevating the head of bed (if nocturnal symptoms)
- symptoms may recur if therapy is discontinued

### Complications
- esophageal stricture disease – scarring can lead to dysphagia (solids)
- esophagitis
- ulcer
- bleeding
- Barrett's esophagus and esophageal adenocarcinoma – gastroscopy is recommended for patients with chronic GERD or symptoms suggestive of complicated disease (e.g. anorexia, weight loss, bleeding, dysphagia)

**Side-Effects of Long-Term Use of Proton Pump Inhibitors**
- Only some (pneumonia, *Clostridium difficile* diarrhea, hypomagnesemia, vitamin B12 deficiency, small bowel bacterial overgrowth) seem to be related to suppressing gastric acid whereas others (fractures, chronic kidney disease, dementia, death) have no apparent pathophysiological relationship
- Stopping proton pump inhibitors can increase gastric acid above baseline by a "rebound effect" causing heartburn even in healthy volunteers
- These associations do not preclude long term use of proton pump inhibitors in patients with esophagitis and peptic ulcer, or those needing gastric protection when taking NSAIDs or anti-platelet drugs, but do emphasize the importance of being as definitive as possible when making these diagnoses and accurately assessing risk-benefit ratios (as is true for all drugs)

## Barrett's Esophagus

### Definition
- metaplasia of normal squamous esophageal epithelium to intestinal columnar epithelium containing-type intestinal mucosa (intestinal metaplasia)

### Etiology
- thought to be acquired via long-standing GERD and consequent damage to squamous epithelium

### Epidemiology
- in North America and Western Europe, 0.5-20% of adults are thought to have Barrett's esophagus
- up to 10% of GERD patients will have already developed BE by the time they seek medical attention
- more common in males, age >50, Caucasians, smokers, overweight, hiatus hernia, and long history of reflux symptoms

### Pathophysiology
- endoscopy shows erythematous epithelium in distal esophagus; diagnosis of BE relies on biopsy demonstrating the presence of specialized intestinal epithelium of any length within the esophagus
- BE predisposes first to premalignant changes characterized as low or high-grade dysplasia, which then progresses to adenocarcinoma

### Significance
- rate of malignant transformation is approximately 0.12% per yr for all BE patients prior to dysplasia
- risk of malignant transformation in high-grade dysplasia is significantly higher; studies have reported a 32-59% transformation rate over 5-8 yr of surveillance
- increased gastric acid secretion is more frequently associated with Barrett's esophagus as opposed to reflux alone

### Treatment
- acid suppressive therapy with high-dose PPI indefinitely (or surgical fundoplication)
- surveillance gastroscopy every 3 yr if no dysplasia
- high grade dysplasia: regular and frequent surveillance with intensive biopsy, endoscopic ablation/resection, or esophagectomy produce similar outcomes; however, evidence increasingly favouring endoscopic ablation with mucosal resection or radiofrequency ablation
- if low grade dysplasia, both surveillance (every 6 mo for 1 yr then annually) and endoscopic ablation/resection are satisfactory options

Up to 25% of patients with Barrett's esophagus do not report symptoms of GERD

**Should Patients with Barrett's Esophagus Undergo Periodic Upper GI Endoscopy for Esophageal Cancer Screening?**
**Impact of Endoscopic Surveillance on Mortality From Barrett's Esophagus - Associated Esophageal Adenocarcinomas**
Gastroenterology 2013;145:312-319
There is no question that Barrett's esophagus (BE) increases the incidence of esophageal adenocarcinoma, which can be recognized early on with a safe procedure, endoscopy. Indeed, because early cancer is often asymptomatic and curable, most clinicians recommend period upper endoscopy. Yet Corley et al. found no difference in endoscopy rates in BE patients who died of esophageal adenocarcinoma compared to BE patients who died of other diseases. Perhaps this result is due to statistics, but as the accompanying editorial emphasizes (Gastroenterology 2013; 145:273-6) at the very least this finding should question the value of a screening program. In fact, there are multiple other lines of evidence indicating that endoscopic surveillance is of marginal benefit at most. Possible explanations for this disappointing finding include: most esophageal adenocarcinomas may not arise from BE, esophageal carcinoma is too rare a cause of death in BE, morbidity from esophageal cancer treatments, or that endoscopic screening is just not that effective in the real world. The situation is analogous to the disappointing value of serum PSA screening for prostate cancer. Therefore, adoption of screening programs require more than theoretical calculations.

# Dysphagia

## Definition
- difficulty swallowing

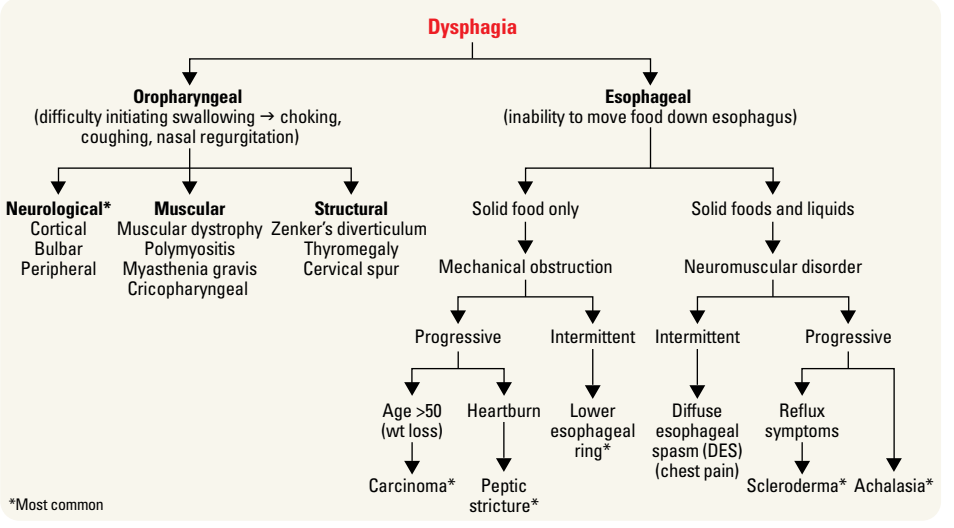



**Figure 4. Approach to dysphagia (eosinophilic esophagitis omitted)**

**Remember:**
**Dysphagia** = Difficulty in swallowing
**Odynophagia** = Pain on swallowing

**Key Questions in Dysphagia**
- Difficulty in starting swallowing?
- Associated symptoms? (regurgitation, change in voice pitch, weight loss)
- Solids, liquids, or both?
- Intermittent or progressive?
- History of heartburn?
- Change in eating habits/diet?

# Esophageal Motor Disorders

## Clinical Features
- dysphagia with solids and liquids
- chest pain (in some disorders)

## Diagnosis
- motility study (esophageal manometry)
- barium swallow sometimes helpful

## Causes
- idiopathic
- achalasia
- scleroderma
- DM
- DES: rare and can be difficult to diagnose due to intermittent presentation

**Table 3. Esophageal Motor Disorder**

| Disorder | Achalasia | Scleroderma | Diffuse Esophageal Spasm |
|---|---|---|---|
| **Definition** | Failure of smooth muscle relaxation at LES<br>Increased LES pressure<br>Progressive loss of peristaltic function | See Rheumatology, RH13<br>Systemic disease characterized by vasculopathy and tissue fibrosis (especially skin thickening) | Normal peristalsis interspersed with frequent, repetitive, spontaneous, high pressure, non-peristaltic waves (tertiary peristalsis) |
| **Etiology** | Usually idiopathic<br>2° or pseudo-achalasia: e.g. malignancy, Chagas disease (*Trypanosoma cruzi*) | Involves autoimmune, genetic, hormonal, and environmental factors<br>Dysphagia: caused by reflux, dysmotility, or both | Idiopathic |
| **Pathophysiology** | Inflammatory degeneration of Auerbach's plexus → increase in LES pressure, incomplete relaxation of LES with swallowing, aperistalsis | Blood vessel damage → intramural neuronal dysfunction → distal esophageal muscle weakening → aperistalsis and loss of LES tone → reflux → stricture → dysphagia | Potential mechanisms include impaired inhibitory innervation to esophageal body, malfunction in endogenous nitric oxide synthesis |
| **Diagnosis** | CXR: no air in stomach, dilated esophagus<br>Barium studies: esophagus terminates in narrowing at LES ("bird's beak")<br>Endoscopy: normal mucosa<br>Manometry: definitive diagnosis (signs listed above) | Clinical features of scleroderma<br>Manometry: decreased pressure in LES, decreased peristalsis in body of esophagus | Barium x-ray: "Corkscrew pattern"<br>Manometry: >30% (but <100%) of esophageal contractions are aperistaltic<br>Endoscopy: normal mucosa |
| **Treatment** | Dilatation of LES with balloon, ± GERD prophylaxis, 50% good response, can repeat, risk of perforation (5%)<br>Injection of botulinum toxin into LES (temporary)<br>POEM (perioral endoscopicmyotomy) | Medical: aggressive GERD therapy (PPIs bid)<br>Surgery: anti-reflux surgery (gastroplasty, last resort) | Reassurance not cardiac pain<br>Medical: nitrates, calcium channel blockers, anticholinergics have variable benefit<br>Surgical: long esophageal myotomy if unresponsive to above treatment (rarely helpful); balloon dilatation |

# Esophageal Diverticula

### Definition
- outpouchings of one or more layers of the esophageal tract

### Clinical Features
- commonly associated with motility disorders
- dysphagia, regurgitation, retrosternal pain, intermittent vomiting, may be asymptomatic

### Classification
- pharyngoesophageal (Zenker's) diverticulum
  - most frequent form of esophageal diverticulum
  - posterior pharyngeal outpouching most often on the left side, above cricopharyngeal muscle and below the inferior pharyngeal constrictor muscle
  - symptoms: dysphagia, regurgitation of undigested food, halitosis (bad breath)
  - treatment: small and asymptomatic: no treatment required, large and symptomatic: endoscopic or surgical myotomy of cricopharyngeal muscle ± surgical excision of sac

# Peptic Stricture (from Esophagitis)

- presents as dysphagia alongside a long history of reflux symptoms, but reflux symptoms may disappear as stricture develops
- diagnosed with endoscopy or barium study if endoscopy contraindicated or unavailable

### Treatment
- endoscopic dilatation and indefinite PPI

# Esophageal Carcinoma

- see General Surgery, GS15

# Webs and Rings

- web = partial occlusion (upper esophagus)
- ring = circumferential narrowing (lower esophagus)

### Clinical Features
- asymptomatic with lumen diameter >12 mm, provided peristalsis is normal
- dysphagia with large food boluses
- Schatzki ring
  - mucosal ring at squamo-columnar junction
  - causes intermittent dysphagia with solids
  - treatment involves disrupting ring with endoscopic dilation



**Plummer-Vinson Syndrome Triad**
- Iron deficiency anemia
- Dysphagia
- Esophageal webs

* rare (prevalence <1 in 1,000,000) but good prognosis when treated with iron and esophageal dilatation

# Infectious Esophagitis

### Definition
- severe mucosal inflammation and ulceration as a result of a viral or a fungal infection

### Risk Factors
- DM
- chemotherapeutic agents
- immunocompromised states

### Clinical Features
- characteristically odynophagia, less often dysphagia

### Appearance
- *Candida* (most common): whitish-yellow plaques without visible ulceration or inflammation
- Herpes (second most common), CMV: focal ulcers

### Investigations
- diagnosis via endoscopic visualization and biopsy

### Treatment
- *Candida*: nystatin swish and swallow, ketoconazole, fluconazole
- Herpes: often self-limiting; acyclovir, valacyclovir, famciclovir
- CMV: IV ganciclovir, famciclovir, or oral valganciclovir



**Eosinophilic Esophagitis**
- Eosinophils infiltrate the epithelium of the esophagus
- Causes odynophagia, dysphagia, common cause of bolus food impaction
- Usually primary, but can be part of the spectrum of eosinophilic gastroenteritis, secondary to drugs, parasites etc.
- Often associated with allergies
- Most characteristically occurs in young men
- Diagnosis established by endoscopic biopsy, suggested by mucosal rings seen in the esophageal mucosa at endoscopy
- Treatment: (a) diet, (b) swallowed corticosteroid nasal spray (fluticasone), (c) swallowed viscous corticosteroid (budesonide mixed with sucralose)

# Stomach and Duodenum

## Dyspepsia

### Definition

- predominant epigastric pain/burning lasting at least 1 mo (predominant associated symptoms are vomiting, weight loss, etc. Differential diagnosis revolves around these more ominous symptoms)
- other symptoms under umbrella of dyspepsia: post-prandial fullness, early satiation
- although the most common cause is functional (investigations show no organic disease but pain persists), sinister disease can present similarly (e.g., pancreatic cancer)

### History and Physical Exam

- history: most important are age, associated symptoms (such as weight loss and vomiting), and drugs (especially NSAIDs)
- physical exam: adenopathy, abdominal mass/organomegaly, Carnett's sign (if pain is due to abdominal wall muscle problem then the pain will increase during muscle contraction, such as during a sit-up)

### Investigations

- consider blood tests including CBC, liver enzymes, calcium, *H. pylori* serology, and ultrasound
- gastroscopy to investigate dyspepsia: most causes of dyspepsia are either functional or diagnosable by either blood tests or proton pump inhibitor trial (for peptic disease); however, gastric cancer should not be missed. Consensus guidelines of the Canadian Association of Gastroenterology/American College of Gastroenterology suggest age should be the chief criteria: gastroscopy if age >60 (and if age <60 or under special circumstances such as risk factors for gastric cancer)

The most common cause of dyspepsia is functional (idiopathic) dyspepsia

**Red Flags of Dyspepsia**
(raise suspicion of gastric malignancy):

- Unintended weight loss
- Persistent vomiting
- Progressive dysphagia
- Odynophagia
- Unexplained anemia or iron deficiency
- Hematemesis
- Jaundice
- Palpable abdominal mass or lymphadenopathy
- Family history of upper GI cancer
- Previous gastric surgery

## Stomach

**Table 4. Cells of the Gastric Mucosa**

| Cell Type | Secretory Product | Important Notes |
|---|---|---|
| **Parietal Cells** | Gastric acid (HCl) and intrinsic factor | Stimulated by histamine, ACh, gastrin |
| **Chief Cells** | Pepsinogen | Stimulated by vagal input and local acid |
| **D-Cells** | Somatostatin | Inhibits release of hormones including gastrin |
| **G-Cells** | Gastrin | Stimulates $H^+$ production from parietal cells |
| **Superficial Epithelial Cells** | Mucus, $HCO_3^-$ | Protect gastric mucosa |

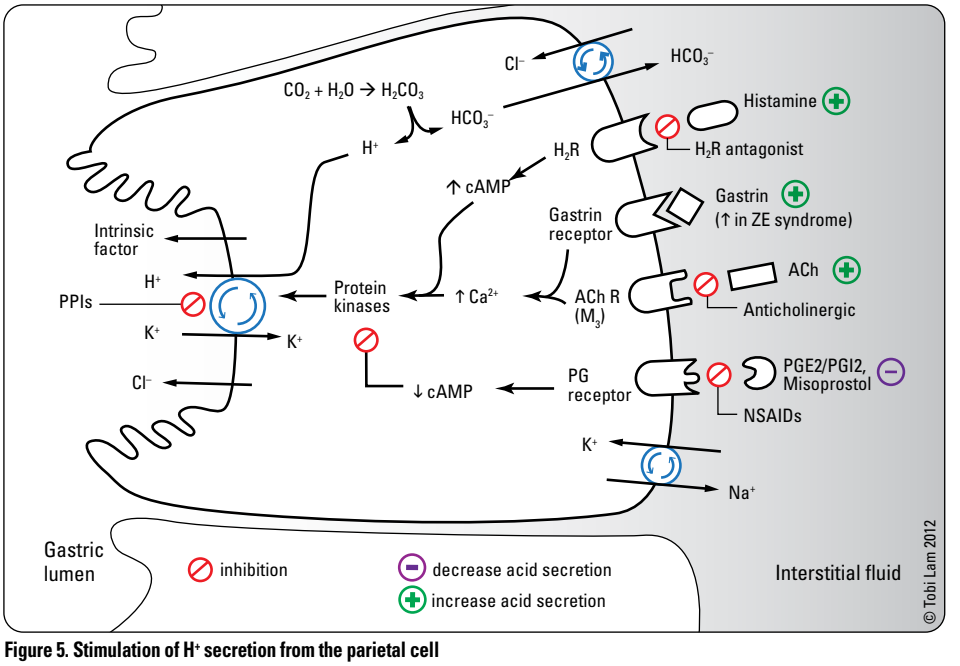



**Figure 5. Stimulation of $H^+$ secretion from the parietal cell**

# Gastritis

## Definition
- defined histologically: inflammation of the stomach mucosa

## Etiology
- some causative agents may play a role in more than one type of gastritis and an individual patient may have histopathological evidence of more than one type of gastritis

**Table 5. Updated Sydney Classification of Gastritis**

| Type | Common Etiology |
|---|---|
| **Acute Gastritis** | |
| Hemorrhagic/erosive gastritis | Alcohol, Aspirin®/NSAID, shock/physiological stress (seen in ICU patients) |
| Helicobacter gastritis | *H. pylori** |
| **Chronic Gastritis** | |
| Non-atrophic | *H. pylori* |
| Atrophic | *H. pylori*, dietary, environmental factors (multi-focal), autoimmunity |
| Chemical | NSAID, bile |
| Radiation | Radiation injury |
| Lymphocytic | Celiac disease, drug |
| Eosinophilic | Food allergies |
| Non-infectious granulomatous | Crohn's disease, sarcoidosis |
| Other infectious gastritides | Bacteria, viruses, fungi, parasite, TB, syphilis |

## Clinical Features
- non-erosive gastritis is asymptomatic (except in certain rare causes like Crohn's disease), does not cause pain; difficult to diagnose clinically or endoscopically – requires biopsy for diagnosis
- erosive gastritis can cause bleeding (pain only if progresses to ulcers – rare); can be seen endoscopically

## Treatment
- determined by etiology (see *H. pylori*, G13, *NSAID*, G13 and *Stress-Induced Ulceration*, G14)
- non-pharmacological: avoidance of mucosal irritants such as alcohol, NSAIDs, and foods that trigger symptoms

# Peptic Ulcer Disease

## Definition
- focal defects in the mucosa that penetrate the muscularis mucosal layer; results in scarring (defects superficial to the muscularis mucosa are erosions and do not cause scarring)
- peptic ulcer disease includes defects located in the stomach (gastric ulcers) and duodenum (duodenal ulcers)

## Etiology

**Table 6. Etiology of Peptic Ulcer Disease**

| | Duodenal | Gastric |
|---|---|---|
| ***H. pylori* Infection** | 90% | 60% |
| **NSAIDs** | 7% | 35% |
| **Physiologic Stress-Induced** | <3% | <5% |
| **Zollinger-Ellison Syndrome** | <1% | <1% |
| **Idiopathic** | 15% | 10% |

- NSAID negative, *H. pylori* negative ulcers becoming more commonly recognized
- others: CMV, ischemic, idiopathic
- alcohol: damages gastric mucosa but rarely causes ulcers
- peptic ulcer associated with cigarette smoking, cirrhosis of liver, COPD, and chronic renal failure

**Cigarette Smoking and PUD**
- Increased risk of ulcer
- Increased risk of complications
- Increased chance of death from ulcer
- Impairs healing

## Clinical Features
- dyspepsia: most common presenting symptom
  - only 5% of patients with dyspepsia have ulcers, while most have functional disease
  - however, 70% of peptic ulcers are asymptomatic
- may present with complications
  - bleeding 10% (severe if from gastroduodenal artery), perforation 2% (usually anterior ulcers), gastric outlet obstruction 2%
  - posterior inflammation (penetration) 2%; may also cause pancreatitis

- duodenal ulcers: 6 classical features, but history alone cannot distinguish from functional dyspepsia
  - epigastric pain; may localize to tip of xiphoid
  - burning
  - develops 1-3 h after meals
  - relieved by eating and antacids
  - interrupts sleep
  - periodicity (tends to occur in clusters of weeks with subsequent periods of remission)
- gastric ulcers: more atypical symptoms; a biopsy is necessary to exclude malignancy

## Investigations

- endoscopy (most accurate)
- upper GI series
- *H. pylori* tests (see Table 7)
- fasting serum gastrin measurement if Zollinger-Ellison syndrome suspected (but most common cause of elevated serum gastrin level is atrophic gastritis)

**Gastric vs. Duodenal Ulcers**
Gastric ulcers must always be biopsied to rule out malignancies; duodenal ulcers are rarely malignant

## Treatment

- specific management depends on etiology; (see *H. pylori*, G13, *NSAID-Induced Ulceration*, G13 and *Stress-Induced Ulceration*, G14)
- treat *H. pylori* infection if present; chief advantage of quadruple therapy is to lower recurrence rate of peptic ulcer disease
- stop NSAIDs if possible
- start PPI: inhibits parietal cell $H^+/K^+$-ATPase pump which secretes acid
  - heals most ulcers, even if NSAIDs are continued
- other medications (e.g. histamine H2-antagonists) less effective
- discontinue cigarette smoking
- no diet modifications required but some people have fewer symptoms if they avoid caffeine, alcohol, and spices

**Approach to PUD**
- Stop NSAIDs
- Acid neutralization
- *H. pylori* eradication
- Quit smoking

## Management of Bleeding Peptic Ulcers

- OGD to explore upper GI tract
- IV pantoprazole continuous drip
- establish risk of rebleeding/continuous bleed (since most ulcers stop bleeding spontaneously)
  - clinical risk factors: increased age (>60), bleeding diathesis, history of PUD, comorbid disease, hemodynamically unstable
  - endoscopic signs of recurrent bleeding (active bleeding, visible vessel, clot, red spot) more predictive than clinical risk factors
    - if ulcer possesses high risk stigmata, then endoscopic therapy should be performed, consider ICU admission

**Bleeding Peptic Ulcers**
**Risk Factors for Increased Mortality**
- Co-existent illness
- Hemodynamic instability
- Age >60 yr
- Transfusion required

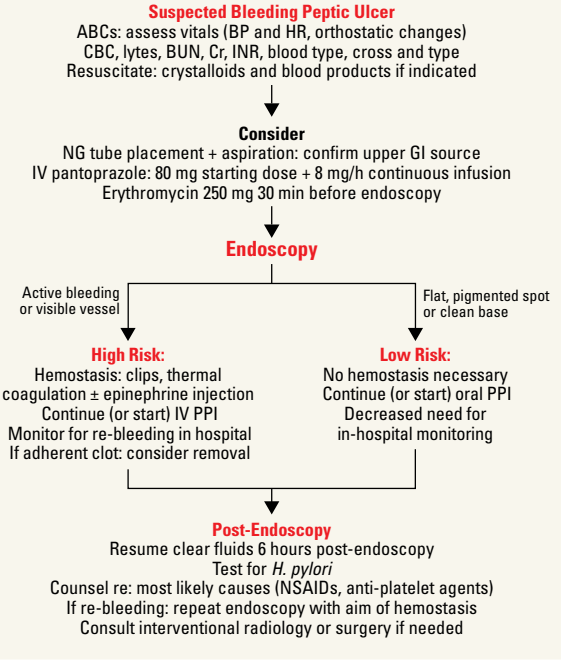



**Figure 6. Approach to management of suspected bleeding peptic ulcer**
Adapted from: Gralnek I, Barkun A, Bardou M. Management of acute bleeding from a peptic ulcer. NEJM 2008;359:928-937

# *H. pylori*-Induced Peptic Ulceration

### Pathophysiology
- *H. pylori*: Gram-negative flagellated rod that resides within the gastric mucosa, causing persistent infection and inflammation
- acid secreted by parietal cells (stimulated by vagal acetylcholine, gastrin, histamine) necessary for most ulcers
- etiology of peptic ulcer disease secondary to *H. pylori* is not well understood; however, the pattern of colonization correlates with outcome
- gastritis only in antrum (15% of patients), high gastric acid, associated with duodenal ulcer, may progress to gastric metaplasia of duodenum where ulcer forms
- gastritis throughout stomach ("pangastritis" – 85% of patients), low gastric acid, associated with stomach ulcer and cancer

### Epidemiology
- *H. pylori* is found in about 20% of all Canadians
- highest prevalence in those raised during 1930s
- infection most commonly acquired in childhood, presumably by fecal-oral route
- high prevalence in developing countries, low socioeconomic status (poor sanitation and overcrowding)

### Outcome
- gastritis (non-erosive) occurs in 100% of patients but is asymptomatic
- peptic ulcer in 15% of patients
- gastric carcinoma and mucosal associated lymphomatous tissue [MALT] lymphoma in 0.5% of patients
- most are asymptomatic but still worthwhile eradicating to lower future risk of peptic ulcer/gastric malignancy and prevent spread to others (mostly children <5 yr of age)

### Diagnosis

**Table 7. Diagnosis of *H. pylori* Infection**

| Test | Sensitivity | Specificity | Comments |
|---|---|---|---|
| **Non-invasive Tests** | | | |
| Urea breath test | 90-100% | 89-100% | Affected by PPI therapy (false negatives) |
| Serology | 88-99% | 89-95% | Can remain positive after treatment |
| Fecal antigen | | | Only rarely used in clinical practice |
| **Invasive Tests (require endoscopy)** | | | |
| Histology | 93-99% | 95-99% | Gold standard; affected by PPI therapy (false negatives) |
| Rapid urease test (on biopsy) | 89-98% | 93-100% | Rapid |
| Microbiology culture | 98% | 95-100% | Research only |

### Treatment: *H. pylori* Eradication
- bismuth quadruple therapy recommended for 10-14 d: PPI (e.g. lansoprazole 30 mg bid) + bismuth 525 mg qid + metronidazole 250 mg qid + tetracycline 500 mg qid
- alternatively, concomitant nonbismuth quadruple therapy for 10-14 d: PPI + amoxicillin + metronidazole + clarithromycin

***Helicobacter pylori* Therapy for the Prevention of Metachronous Gastric Cancer**
N Engl J Med 2018;378:1085-1095
**Purpose**: To evaluate the role of *H. pylori* eradication in the prevention of metachronous gastric cancer.
**Study**: Double-blinded randomized controlled trial.
**Population**: 470 patients with a subtotal gastrectomy for gastric cancer and *H. pylori* infection with or without antibiotic treatment.
**Outcome**: Incidence of metachronous gastric cancer.
**Results**: After almost 6 yr, 7.2% of the antibiotics-treated group developed another cancer in the gastric remnant vs. 13.4% in the placebo control group.
**Conclusions**: This provides definitive evidence that *H. pylori* is worthwhile treating no matter how advanced the gastric carcinogenic process.

# NSAID-Induced Ulceration

- NSAID use causes gastric mucosal petechiae in virtually all, erosions in most, ulcers in some (25%)
- erosions bleed, but usually only ulcers cause significant clinical problems
- most NSAID ulcers are clinically asymptomatic: dyspepsia is as common in patients with ulcers as in patients without ulcers; NSAID-induced ulcers characteristically present with complications (bleeding, perforation, obstruction)
- NSAIDs more commonly cause gastric ulcers than duodenal ulcers
- may exacerbate underlying duodenal ulcer disease

### Pathophysiology
- direct: erosions/petechiae – are due to local (direct) effect of drug on gastric mucosa
- indirect: systemic NSAID effect (intravenous NSAID causes ulcers, but not erosions). NSAIDs also inhibit mucosal cyclooxygenase, leading to decreased prostaglandin synthesis. This results in ulcers from reduced secretion of protective bicarbonate and mucous, and decreased mucosal blood flow

### Risk Factors for NSAID-induced Peptic Ulcer
- previous peptic ulcers/upper GI bleed
- age (≥65 yr)
- high dose of NSAID/multiple NSAIDs being taken
- concomitant corticosteroid use
- concomitant cardiovascular disease/other significant diseases

### Treatment
- prophylactic cytoprotective therapy with a PPI is recommended if any of the above risk factors exist concomitantly with ASA/NSAID use
- lower NSAID dose or stop all together and replace with acetaminophen
- combine NSAID with PPI or misoprostol (less effective) in one tablet
- enteric coating of Aspirin® (ECASA) provides minor benefit since this decreases incidence of erosion, not incidence of ulceration



If at high risk for development of ulcers, prophylaxis with PPI indicated

## Stress-Induced Ulceration

### Definition
- ulceration or erosion in the upper GI tract of ill patients, usually in ICU (stress is physiological, not psychiatric)
- lesions most commonly in fundus of stomach

### Pathophysiology
- unclear: likely involves ischemia; may be caused by CNS disease, acid hypersecretion, Cushing's ulcers
- mechanical ventilation is the most important risk factor

### Risk Factors
- mechanical ventilation
- anti-coagulation
- multi-organ failure
- septicemia
- severe surgery/trauma
- CNS injury ("Cushing's ulcers")
- burns involving more than 35% of body surface



**Curling's and Cushing's Ulcers**
- **Curling's ulcer**: acute peptic ulcer of the duodenum resulting as a complication from severe burns when reduced plasma volume leads to ischemia and cell necrosis (sloughing) of the gastric mucosa (think BURN from a CURLing iron)
- **Cushing's ulcer**: peptic ulcer produced by elevated intracranial pressure (may be due to stimulation of vagal nuclei secondary to elevated ICP which leads to increased secretion of gastric acid)

### Clinical Features
- UGIB (see *Upper Gastrointestinal Bleeding*, G28)
- painless

### Treatment
- prophylaxis with gastric acid suppressants decreases risk of UGIB; PPI most potent but may increase risk of pneumonia; H2 blockers less potent but less likely to cause pneumonia
- treatment same as for bleeding peptic ulcer but often less successful

## Gastric Carcinoma

- see General Surgery, GS24

# Small and Large Bowel

## Classification of Diarrhea

### Definition
- clinically: diarrhea defined as stools that are looser and/or more frequent than normal (i.e. ≥3x/d); physiologically: 24 h stool weight >200 g (less useful clinically)

### Classification
- acute vs. chronic
- small volume (tablespoons of stool; typical of colonic diseases) vs. large volume (>1/2 cup stool; typical of small bowel diseases)
- watery: secretory (diarrhea persists with fasting) vs. osmotic (diarrhea stops with fasting)
- steatorrhea
- inflammatory
- functional

# Acute Diarrhea

• see Pediatrics, P37

## Definition
• passage of ≥3 loose or liquid stools/d OR >200 g stool/d for >2 d but ≤14 d

## Epidemiology
• one of the top five leading causes of death worldwide, according to the World Health Organization
• significant morbidity in developed countries (over 900,000 hospitalizations in the United States each year)

## Etiology
• most commonly due to infections
• most infections are self-limiting and resolve within 7 d

## Risk Factors
• food (raw or undercooked meat and seafood, unpasteurized dairy products)
• medications: antibiotics, laxatives
• others: high risk sexual activity, infectious outbreaks, occupational exposures (daycare workers), family history (IBD)

## Approach to Acute Diarrhea
• the vast majority of acute diarrhea is caused by infection
• in most cases, acute diarrheal illness is viral and/or self-limited, and lasts <3 d
• investigations are costly and are necessary only in certain circumstances
  ▪ therefore, evaluation of acute diarrhea involves identifying characteristics of the patient or illness that warrant further investigation and assessing volume status to determine appropriate method of rehydration

## Physical Exam
• volume status: appearance, level of alertness, pulse, BP, orthostatic vitals, JVP, mucous membranes, skin turgor, capillary refill
• abdominal exam: pain, guarding, peritoneal signs

**Table 8. Classification of Acute Diarrhea**

| | Inflammatory | Non-Inflammatory |
|---|---|---|
| **Definition** | Disruption of intestinal mucosa | Intestinal mucosa intact |
| **Site** | Usually colon | Usually small intestine |
| **Mechanism** | Organisms and cytotoxins invade mucosa, killing mucosal cells, and further perpetuating the diarrhea | Stimulation of intestinal water secretion and inhibition of water absorption (i.e. secretory problem) |
| **Sigmoidoscopy** | Usually abnormal mucosa seen | Usually normal |
| **Symptoms** | Bloody (not always)<br>Small volume, high frequency<br>Often lower abdominal cramping with urgency ± tenesmus<br>May have fever ± shock | Watery, little or no blood<br>Large volume<br>Upper/periumbilical pain/cramp ± shock |
| **Investigations** | Fecal WBC and RBC positive | Fecal WBC negative |
| **Etiology** | See *Differential Diagnosis of Presenting Complaints*, G4 | See *Differential Diagnosis of Presenting Complaints*, G4 |
| **Differential Diagnosis** | Acute presentation of idiopathic inflammatory bowel disease | Acute presentation of non-inflammatory chronic diarrhea (e.g. celiac disease) |
| **Significance** | Higher yield with stool C&S<br>Can progress to life-threatening megacolon, perforation, hemorrhage<br>Antibiotics may benefit | Lower yield with stool C&S<br>Chief life-threatening problem is electrolyte disturbances/ fluid depletion<br>Antibiotics unlikely to be helpful |

## Investigations
• stool cultures/microscopy (C&S/O&P) are required only if diarrhea is inflammatory, severe, or for epidemiological purposes (daycare worker, nursing home resident, community outbreaks, e.g. Walkerton, etc.)
  ▪ C&S only tests *Campylobacter, Salmonella, Shigella, E. coli*
    ◆ other organisms must be ordered separately
• flexible sigmoidoscopy (without bowel preparation): useful if inflammatory diarrhea suspected
  ▪ biopsies are the most useful method of distinguishing idiopathic IBD (Crohn's disease and ulcerative colitis) from infectious colitis or acute self-limited colitis
• *C. difficile* toxin: indicated when recent/remote antibiotic use, hospitalization, nursing home, or recent chemotherapy

**Useful Questions in Acute Diarrhea**

**Those Fads Wilt**
**T**ravel
**H**omosexual contacts
**O**utbreaks
**S**eafood
**E**xtra-intestinal signs of IBD
**F**amily history
**A**ntibiotics
**D**iet
**S**teatorrhea
**W**eight loss
**I**mmunosuppressed
**L**axatives
**T**umour history

**Infectious Causes of Inflammatory Diarrhea**

**Your Stool Smells Extremely Crappy**
***Y**ersinia*
***S**higella*
***S**almonella*
***E**. coli* (EHEC 0157:H7), ***E**. histolytica*
***C**ampylobacter, **C**. difficile*

**Finally: A Role for Bacteriotherapy**
**Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile***
NEJM 2013; 368:407-15
For centuries, out-of-the-box thinkers have speculated that the colonic bacteria all of us have, but which differs among individuals, play a role in disease. More recently, the colonic microbiome has become the hottest area of research in gastroenterology. The best documented medical indication for manipulating the colonic bacteria is recurrent *C. difficile* infection. In this randomized study of this disease, infusion of donor feces via a nasoduodenal tube resolved diarrhea in 81% of patients, without side-effects, compared to 31% given the standard treatment of oral vancomycin, and 23% of patients given oral vancomycin plus bowel lavage. It takes little prescience to predict an onslaught of future studies investigating the therapeutic potential of altering the human microbiome.

## Treatment

- fluid and electrolyte replacement orally in most cases, intravenous if severe extremes of age/coma
- anti-diarrheals
  - antimotility agents: diphenoxylate, loperamide (Imodium®); contraindicated in mucosal inflammation
    - side effects: abdominal cramps, toxic megacolon
  - absorbants: kaolin/pectin (Kaopectate®), methylcellulose, activated attapulgite
    - act by absorbing intestinal toxins/micro-organisms, or by coating intestinal mucosa
    - much less effective than antimotility agents
  - modifiers of fluid transport: bismuth subsalicylate (Pepto-Bismol®) may be helpful (but should not be used in the presence of bloody diarrhea or fever)
- antibiotics: rarely indicated
  - risks
    - prolonged excretion of enteric pathogen (especially *Salmonella*)
    - drug side effects (including *C. difficile* infection)
    - development of resistant strains
    - renal failure/hemolysis (enterohemorrhagic *E. coli* O157:H7)
  - indications for antimicrobial agents in acute diarrhea
    - septicemia
    - prolonged fever with fecal blood or leukocytes
    - clearly indicated: *Shigella, V. cholerae, C. difficile*, traveller's diarrhea (enterotoxigenic *E. coli* [ETEC]), *Giardia, Entamoeba histolytica, Cyclospora*
    - situational: *Salmonella, Campylobacter, Yersinia*, non-enterotoxigenic *E. coli*
    - *Salmonella*: always treat *Salmonella typhi* (typhoid or enteric fever); treat other *Salmonella* only if there is underlying immunodeficiency, hemolytic anemia, extremes of age, aneurysms, prosthetic valve grafts/joints, sickle cell disease

**Causes of Acute Bloody Diarrhea**
**CHESS**
***C****ampylobacter*
**H**emorrhagic *E. coli* (e.g. O157:H7)
***E****ntamoeba histolytica*
***S****almonella*
***S****higella*

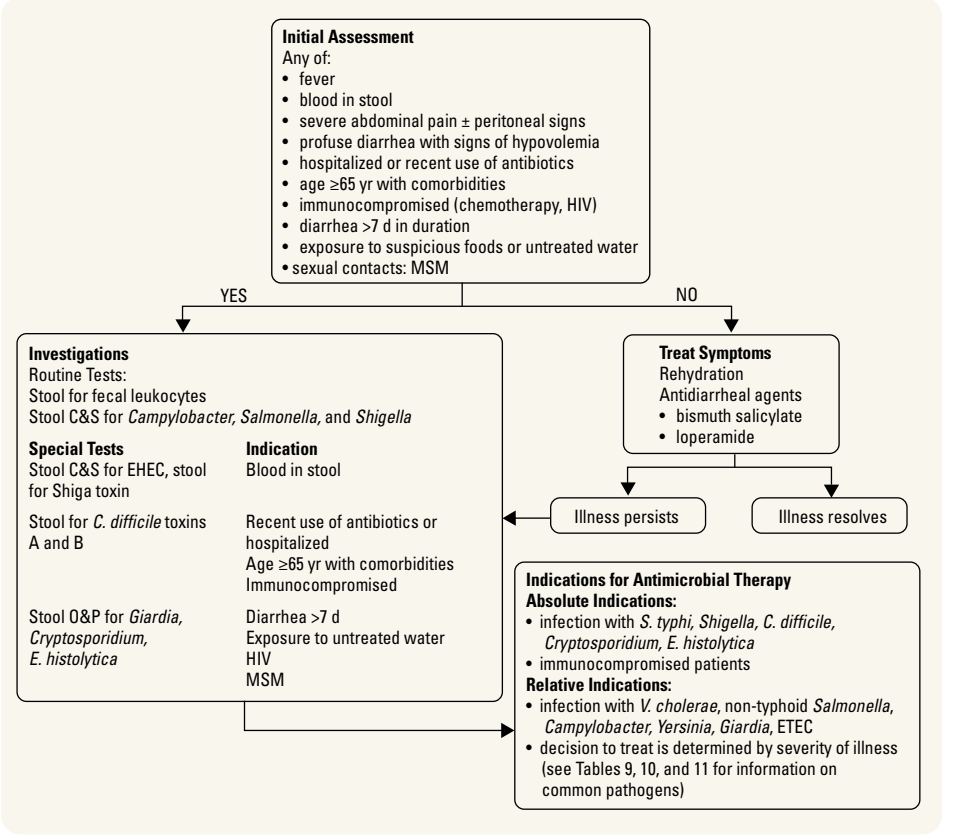



**Figure 7. Approach to acute diarrhea**
Note: *S. typhi* has a rose spot rash (transient maculopapular rash on anterior thorax, upper abdomen), and a prodrome of high fever, bradycardia, headache, and abdominal pain. Diarrhea is not the initial presentation

**Table 9. Bacteria in Infectious Diarrhea**

| Pathogen | Source or Mode of Transmission | Incubation | Clinical Features | | | | Duration | Antimicrobial Therapy | Notes |
|---|---|---|---|---|---|---|---|---|---|
| | | | Fever | Bloody Stool | Abdo Pain | Nausea/ vomiting | | | |
| ***B. cereus* – Type A (emetic)** | Rice dishes | 1-6 h | – | – | – | + | <12 h | None | Preformed exotoxin |
| ***B. cereus* – Type B (diarrheal)** | Meats, vegetables, dried beans, cereals | 8-16 h | – | – | – | – | <24 h | None | Secondary endotoxin |
| ***Campylobacter jejuni*** | Uncooked meat, especially poultry | 2-10 d | + | ± | + | ± | <1 wk | Macrolide or fluoroquinolone if diarrhea >1 wk, bloody diarrhea, or immunocompromised | Most common bacterial cause of diarrhea in Canada<br>Associated with Guillain-Barré syndrome |
| ***Clostridium difficile*** | Can be normally present in colon in small numbers (primary risk factor for disease is exposure to antimicrobials) | Unclear | ± | ± | ± | – | Variable | Stop culprit antibiotic therapy, if possible<br>Supportive therapy (IV fluids)<br>Empiric treatment with either vancomycin or fidaxomicin<br>If access to empiric treatment is limited, then metronidazole may be used<br>For fulminant C. difficile infection (previously called severe), oral vancomycin is used. IV metronidazole added to regimen if ileus present | Usually follows antibiotic treatment (especially clindamycin, fluoroquinolones, penicillins, cephalosporins)<br>Can develop pseudomembranous colitis |
| ***Clostridium perfringens*** | Contaminated food, especially meat and poultry | 8-12 h | ± | – | + | – | <24 h | None | Clostridium spores are heat resistant<br>Secondary enterotoxin<br>Enteroinvasive |
| ***E. coli* (EIEC)** | Contaminated food/ water | 1-3 d | + | ± | + | – | 7-10 d | None | Relatively uncommon<br>Enterotoxigenic |
| ***E. coli* (ETEC)** | Contaminated food/ water | 1-3 d | – | – | + | – | 3 d | Fluoroquinolone or azithromycin for moderate to severe symptoms | Most common cause of traveller's diarrhea<br>Heat-labile and heat-stable toxins |
| **Enterohemorrhagic *E. coli* (EHEC/STEC) i.e. O157:H7** | Contamination of hamburger, raw milk, drinking, and recreational water | 3-8 d | – | + | + | ± | 5-10 d | None: antibiotics increase risk of HUS | Shiga toxin production<br>Monitor renal function:10% develop HUS<br>Antidiarrheals increase risk of HUS |
| ***Salmonella Typhi S. Paratyphi* (i.e. Enteric Fever, Typhoid)** | Fecal-oral<br>Contaminated food/ water<br>Travel to endemic area | 10-14 d | + | ± | + | ± | <5-7 d | Empiric treatment with ceftriaxone, ciprofloxacin, or azithromycin<br>Fluoroquinolone resistance is increasing | Salmonella typhi: "Rose spot" rash (on anterior thorax, upper abdomen), fever, and abdominal pain precedes diarrhea |
| **Non-typhoidal *Salmonellosis S. Typhimurium, S. Enteritidis*** | Contaminated animal food products, especially eggs, poultry, meat, milk | 12-72 h | + | ± | + | + | 3-7 d | Ciprofloxacin only in severe illness, extremes of age, joint prostheses, valvular heart disease, severe atherosclerosis, cancer, uremia | |
| ***Shigella dysenteriae*** | Fecal-oral<br>Contaminated food/ water | 1-4 d | + | ± | + | + | <1 wk | Fluoroquinolone | Very small inoculum needed for infection<br>Complications include toxic megacolon, HUS<br>Antidiarrheals may increase risk of toxic megacolon |
| ***Staphylococcus aureus*** | Unrefrigerated meat and dairy products (custard, pudding, potato salad, mayo) | 2-4 h | – | – | + | + | 1-2 d | None | Heat-stable preformed exotoxin |
| ***Vibrio cholerae*** | Contaminated food/ water, especially shellfish | 1-3 d | – | – | – | – | 3-7 d | Tetracycline or quinolones (ciprofloxacin) | Massive watery diarrhea (1-3 L/d)<br>Mortality <1% with treatment |
| ***Yersinia*** | Contaminated food<br>Unpasteurized milk | 5 d | + | ± | + | ± | Up to 3 wk | Fluoroquinolone only for severe illness | Majority of cases in children 1-4 yr<br>Mesenteric adenitis and terminal ileitis can occur without diarrhea, mimicking appendicitis |

**Table 10. Parasites in Infectious Diarrhea**

| Pathogen | Source or Mode of Transmission | Incubation | Clinical Features | | | | Duration | Antimicrobial Therapy | Notes |
|---|---|---|---|---|---|---|---|---|---|
| | | | Fever | Bloody Stool | Abdo Pain | Nausea/ vomiting | | | |
| ***Cryptosporidium*** | Fecal-oral | 7 d | ± | – | – | + | 1-20 d | Paromomycin + nitazoxanide | Immune reconstitution if immunosuppressed |
| ***Entamoeba histolytica*** | Worldwide endemic areas<br>Fecal-oral | 2-4 wk | ± | + | – | + | Variable | Metronidazole + iodoquinol or paromomycin if symptomatic infection<br>Only iodoquinol or paromomycin for asymptomatic cyst passage | If untreated, potential for liver abscess<br>Sigmoidoscopy shows flat ulcers with yellow exudates |
| ***Giardia lamblia*** | Fecal-oral<br>Contaminated food/ water | 1-4 wk | – | – | + | + | Variable | Metronidazole or nitazoxanide Treatment of asymptomatic carriers NOT recommended | Higher risk in: daycare children, intake of untreated water ("beaver fever"), MSM, immunodeficiency (decreased IgA)<br>May need duodenal biopsy |

**Table 11. Viruses in Infectious Diarrhea**

| Pathogen | Source or Mode of Transmission | Incubation | Clinical Features | | | | Duration | Antimicrobial Therapy | Notes |
|---|---|---|---|---|---|---|---|---|---|
| | | | Fever | Bloody Stool | Abdo Pain | Nausea/ vomiting | | | |
| **Norovirus** | Fecal-oral | 24 h | – | – | + | + | 24 h | None | Noroviruses includes Norwalk virus |
| **Rotavirus** | Fecal-oral | 2-4 d | ± | – | – | ± | 3-8 d | None | Can cause severe dehydration<br>Virtually all children are infected by 3 yr of age<br>Oral vaccine given at 2 and 4 mo of age |

# Traveller's Diarrhea



## Epidemiology
- most common illness to affect travellers
- up to 50% of travellers to developing countries affected in first 2 wk and 10-20% after returning home

## Etiology
- bacterial (80-90%): *E. coli* most common (ETEC), *Campylobacter, Shigella, Salmonella, Vibrio* (non-cholera); wide regional variation (e.g. Campylobacter more common in Southeast Asia)
- viral: norovirus, rotavirus, and astrovirus account for 5-8%
- protozoal (rarely): *Giardia, Entamoeba histolytica, Cryptosporidium*, and *Cyclospora* for ~10% in long-term travellers
- pathogen-negative traveller's diarrhea common despite exhaustive microbiological workup

## Treatment
- rehydration is the mainstay of therapy
  - rehydrate with sealed beverages
  - in severe fluid loss, use oral rehydration solutions (1 package in 1 L boiled or treated water)
- treat symptoms: antidiarrheal agents (e.g. rifamycin antibiotics, bismuth salicylate, loperamide)
- empiric antibiotics in moderate or severe illness: ciprofloxacin or azithromycin or rifaximin
  - note: there is increasing fluoroquinolone resistance in causative agents, especially in South and Southeast Asia

## Prevention
- proper hygiene practices
  - avoid consumption of: foods or beverages from establishments with unhygienic conditions (e.g. street vendors), raw fruits or vegetables without a peel, raw or undercooked meat and seafood
  - avoid untreated water
- bismuth salicylate (Pepto-Bismol®): 60% effective (2 tablets qid according to CDC website)
- CDC Guidelines: antibiotic prophylaxis not recommended
  - increased risk of infection with resistant organisms
  - high risk groups (e.g. immunocompromised) likely to be infected with pathogen not covered by standard antimicrobial agents

- Dukoral®: oral vaccine that offers protection against *V. cholerae* (efficacy ~80%) and ETEC (efficacy ~50-67%)
  - Public Health Agency of Canada recommends that it may be considered for the following situations (not recommended for routine use in travellers):
    - short-term travellers >2 yr old who are high-risk (e.g. chronic illness) for whom there is an increased risk of serious consequences for traveller's diarrhea (e.g. chronic renal failure, CHF, type 1 DM, inflammatory bowel disease)
    - immunosuppressed
    - history of repeat traveller's diarrhea
    - increased risk of acquiring traveller's diarrhea (gastric hypochlorhydria or young children >2 yr)
    - travellers to cholera endemic countries at increased risk of exposure
- two vaccines against *Salmonella typhi* are available and their effectiveness is estimated to be between 50-70%

# Chronic Diarrhea



### Definition
- passage of frequent unformed stool for >4 wk (persistent diarrhea as 14-30 d)
- approach is similar to that of acute diarrhea except that the majority of cases are non-infectious

### Etiology/Classification
- see *Differential Diagnosis of Common Presenting Complaints*, G4

### Investigations
- guided by history
- stool analysis for: *C. difficile* toxin, C&S, O&P ± fecal fat, WBC
- blood for: CBC, electrolytes, CRP, TSH, celiac serology (IgA anti-tTG; ask for serum protein electrophoresis or immunoglobulin quantitation to rule out IgA deficiency which has an increased frequency in celiac disease)
- colonoscopy and ileoscopy with biopsy
- upper GI endoscopy with duodenal biopsy
- wireless small bowel endoscopy capsule (low yield)
- trial of lactose free diet
  - caveat: may delay diagnosis of IBD and celiac disease

# Maldigestion and Malabsorption

### Definition
- maldigestion: inability to break down large molecules in the lumen of the intestine into their component small molecules
- malabsorption: inability to transport molecules across the intestinal mucosa into circulation

### Etiology
- maldigestion
  - inadequate mixing of food with enzymes (e.g. post-gastrectomy)
  - pancreatic exocrine deficiency
  - primary diseases of the pancreas (e.g. cystic fibrosis [remember CF can result in pancreatic exocrine insufficiency as well], pancreatitis, cancer)
  - bile salt deficiency
    - terminal ileal disease (impaired recycling in view of loss greater than synthesis), bacterial overgrowth (deconjugation of bile salts), rarely liver disease (cholestatic, e.g. primary biliary cirrhosis)
  - specific enzyme deficiencies (e.g. lactase)
- malabsorption
  - inadequate absorptive surface
    - infections/infestations (e.g. Whipple's disease, Giardia)
    - immunologic or allergic injury (e.g. celiac disease)
    - infiltration (e.g. lymphoma, amyloidosis)
    - fibrosis (e.g. systemic sclerosis, radiation enteritis): fibrosis can lead to loss of surface area but also areas of stasis with small bowel overgrowth
    - small bowel resection (length, site, location, presence/absence of ileocecal valve and integrity of colon are important)
    - congenital (e.g. short bowel syndrome)
    - inflammatory: extensive ileal Crohn's disease (pivotal number is 100 cm as <100 cm = bile salt or choleretic diarrhea, >100 cm = fatty diarrhea or steatorrhea)
  - drug-induced
    - cholestyramine, ethanol, neomycin, tetracycline, and other antibiotics
  - endocrine
    - DM (complex pathogenesis)

## Clinical Features

- symptoms usually vague unless disease is severe
- weight loss, diarrhea, steatorrhea, weakness, fatigue
- manifestations of malabsorption/deficiency

**Fat Soluble Vitamins: ADEK**
vitamin **A**, vitamin **D**, vitamin **E**, vitamin **K**

**Table 12. Absorption of Nutrients and Fat Soluble Vitamins**

| Deficiency | Absorption | Clinical Disease and/or Features | Investigations |
|---|---|---|---|
| **Iron** | Duodenum, upper jejunum | Hypochromic, microcytic anemia, glossitis, koilonychia (spoon nails), pica | ↓ Hb, ↓ serum Fe, ↓ serum ferritin |
| **Calcium** | Duodenum, upper jejunum (binds to $Ca^{2+}$ binding-protein in cells; levels increased by Vit D) | Metabolic bone disease, may get tetany and paresthesias if serum calcium falls (see Endocrinology, E39) | ↓ serum $Ca^{2+}$, ↓ serum $Mg^{2+}$, and ↑ ALP<br>Evaluate for ↓ bone mineralization radiographically (DEXA) |
| **Folic Acid** | Jejunum | Megaloblastic anemia, glossitis, ↓ red cell folate (may see ↑ folic acid with bacterial overgrowth) | ↓ serum folic acid |
| **Vitamin $B_{12}$** | $B_{12}$ ingested and bound to R proteins mainly from salivary glands; stomach secretes intrinsic factor (IF) in acidic medium; in basic medium, proteases from the pancreas cleave R protein and $B_{12}$-IF complex forms, protecting $B_{12}$ from further protease attack; $B_{12}$ absorbed in ileum and binds to transcobalamin (TC) | Subacute combined degeneration of the spinal cord, peripheral/optic neuropathy, dementia, megaloblastic anemia, glossitis | Differentiate causes by nuclear Schilling test (when available)<br>Positive anti-intrinsic factor antibodies and atrophic gastritis point toward pernicious anemia (see Hematology, H24) |
| **Carbohydrate** | Complex polysaccharides hydrolyzed to oligosaccharides, and disaccharides by salivary and pancreatic enzymes<br>Monosaccharides absorbed in duodenum/jejunum | Generalized malnutrition, weight loss, flatus, and diarrhea | Hydrogen breath test<br>Trial of carbohydrate-restricted diet<br>D-xylose test |
| **Protein** | Digestion at stomach, brush border, and inside cell<br>Absorption occurs primarily in the jejunum | General malnutrition and weight loss, amenorrhea, and ↓ libido if severe | ↓ serum albumin (low sensitivity) |
| **Fat** | Lipase, colipase, phospholipase A (pancreatic enzymes), and bile salts needed for digestion<br>Products of lipolysis form micelles which solubilize fat and aid in absorption<br>Absorption occurs primarily in the jejunum<br>Fatty acids diffuse into cell cytoplasm | Generalized malnutrition, weight loss, and diarrhea<br>Foul-smelling feces + gas<br>Steatorrhea | Small bowel biopsy<br>MRCP, ERCP, pancreatic function tests (not routinely available)<br>Quantitative stool fat test (72 h)<br>May start with qualitative stool fat test (Sudan stain of stool)<br>C-triolein breath test (not routinely available) |
| **Vitamin A** | Dietary sources (e.g. milk, eggs, liver, carrots, sweet potatoes) | Night blindness<br>Dry skin<br>Keratomalacia | |
| **Vitamin D** | Skin (via UV light) or diet (e.g. eggs, fish oil, fortified milk) | Osteomalacia in adults<br>Ricketts in children | |
| **Vitamin E** | Dietary sources (e.g. vegetable oils, nuts, leafy green vegetables) | Retinopathy, neurological problems | |
| **Vitamin K** | Synthesized by intestinal flora<br>↑ risk of deficiency after prolonged use of broad spectrum antibiotics and/or starvation | Prolonged INR may cause bleeding | |

* Calcium malabsorption more commonly causes decreased bone density rather than hypocalcemia because serum calcium levels are protected by leaching calcium from the bone

## Investigations

- tissue transglutaminase (tTG) antibody serology/immunoglobulin A quantitation and abdominal imaging are most useful because celiac disease and chronic pancreatitis are the two most common causes of steatorrhea
- 72 h stool collection (weight, fat content) documents steatorrhea (gold standard)
- fecal elastase to screen for pancreatic insufficiency and/or consider empiric trial of pancreatic enzymes based on clinical context
- serum carotene (precursor to vitamin A), folate, Ca2+, Mg2+, vitamin B12, albumin, ferritin, serum iron solution, INR/PTT
- stool fat globules on fecal smear stained with Sudan (used as an initial screening tool)
- other tests specific for etiology (e.g. CT scan/MRI to visualize pancreas)

## Treatment

- dependent on underlying etiology

# Celiac Disease (Gluten Enteropathy/Sprue)

## Definition
- abnormal small intestine mucosa due to intestinal reaction to gluten, a protein found in wheat, barley, rye, and possibly oats (certified gluten-free oats may be acceptable in a subgroup of patients)

## Etiology
- the only autoimmune disease in which autoantigen (various gliadin peptides) is recognized
- associated with other autoimmune diseases, especially Sjögren's, thyroid disease, DM Type 1
- gluten is broken down to gliadin, which is the toxic factor
- HLA-DQ2 (chromosome 6) found in 80-90% of patients compared with 20% in general population; celiac also associated with HLA-DQ8 (note: up to 40% of Caucasians carry the HLA alleles, but will never develop celiac disease)

## Epidemiology
- more common in women
- family history: 10-15% of first-degree relatives
- may present any time from infancy (when cereals introduced) to elderly
- peak presentation in infancy

## Clinical Features
- classic presentation: diarrhea, weight loss, anemia, symptoms of vitamin/mineral deficiency, failure to thrive; more common current presentation: bloating, gas, iron deficiency
- improves with gluten-free diet, deteriorates when gluten reintroduced
- disease is usually most severe in proximal bowel
  - iron, calcium, and folic acid deficiency (proximal absorption) more common than vitamin B12 deficiency (absorbed in ileum)
- gluten enteropathy may be associated with dermatitis herpetiformis skin eruption, epilepsy, myopathy, depression, paranoia, infertility, bone fractures/metabolic bone disease

## Investigations
- serological tests
  - serum anti-tTG antibody, IgA, is 90-98% sensitive, 94-97% specific
  - patients with selective IgA deficiency have false-negative anti-tTG
    - therefore, measure serum IgA concomitantly (via serum immunoglobulin quantitation)
- incorporate serum testing tTG and/or DGP IgG in IgA deficiencies
- small bowel mucosal biopsy (usually duodenum) is diagnostic with increased intraepithelial lymphocytes (earliest pathologic finding)
  - crypt hyperplasia
  - villous atrophy
  - note: villous atrophy also seen in small bowel overgrowth, Crohn's, lymphoma, Giardia, HIV
- improvement with a gluten-free diet, but should not be started before serological tests and biopsy
- consider CT enterography to visualize small bowel to rule out lymphoma
- evidence of malabsorption (localized or generalized)
  - steatorrhea
  - low levels of ferritin/iron saturation, $Ca^{2+}$, Fe, albumin, cholesterol, carotene, B12 absorption
- quantitative fecal fat >7%

## Treatment
- dietary counselling
  - gluten free diet; avoid barley, rye, wheat (as these grains are related and also have toxic factor, similar to gliadin)
  - oats allowed if not contaminated by other grains (grown in soil without cross-contamination)
  - rice and corn flour are acceptable
  - iron, folate supplementation (with supplementation of other vitamins as needed)
- if poor response to diet change, consider
  - alternate diagnosis
  - non-adherence to gluten-free diet
  - concurrent disease (e.g. microscopic colitis, pancreatic insufficiency)
  - development of intestinal (enteropathy-associated T-cell) lymphoma (abdominal pain, weight loss, palpable mass)
  - development of diffuse intestinal ulceration, characterized by aberrant intraepithelial T-cell population (precursor to lymphoma)



**Gluten Found in BROW**
**B**arley
**R**ye
**O**ats (controversial)
**W**heat

## Prognosis
- associated with increased risk of lymphoma, carcinoma (e.g. small bowel and colon; slight increase compared with general population), autoimmune diseases
- risk of lymphoma may be lowered by dietary gluten restriction

# Inflammatory Bowel Disease

## Definition

- complex, multifactorial etiology
- most likely a sustained response of the immune system, perhaps to enteric flora
- lack of appropriate down-regulation of immune responsiveness after an infection in a genetically predisposed individual

## Genetics

- increased risk of both UC and CD in relatives of patients with either disease, especially siblings, early onset disease
  - familial risk greater if proband has CD rather than UC
- likely polygenomic pattern: 9 gene loci are associated
- CARD15/NOD2 gene mutation associated with CD (relative risk in heterozygote is 3, in homozygote is 40), especially in Ashkenazi Jews, early onset disease, ileal involvement, and fistulizing, fibrostenotic or structuring disease
  - CARD15 gene product modulates NFκβ, which is required for the innate immune response to microbial pathogens, best expressed in monocytes-macrophages

## Clinical Features

**Table 13. Clinical Differentiation of Ulcerative Colitis from Crohn's Disease**

| | Crohn's Disease | Ulcerative Colitis |
|---|---|---|
| **Location** | Any part of GI tract<br>Small bowel + colon: 50%<br>Small bowel only: 30%<br>Colon only: 20% | Isolated to large bowel<br>Always involves rectum, may progress proximally |
| **Rectal Bleeding** | Uncommon; possible if colonic disease | Very common (90%) |
| **Diarrhea** | Less prevalent, large volume, watery<br>Usually non-bloody (may be bloody, particularly if distal colonic involvement) | Frequent, mucous, bloody, small volume stools |
| **Abdominal Pain** | Post-prandial/colicky | Uncommon; predefecation |
| **Fever** | Common | Uncommon |
| **Urgency/Tenesmus** | Uncommon (unless rectum involved) | Common |
| **Palpable Mass** | Frequent (25%), RLQ | Rare (if present, often related to cecum full of stool) |
| **Recurrence After Surgery** | Common | None post-colectomy (with permanent ileostomy) |
| **Endoscopic Features** | Segmental inflammation, ulcers (aphthous, stellate, linear), patchy lesions, pseudopolyps, cobblestoning | Continuous diffuse inflammation, erythema, friability, loss of normal vascular pattern, pseudopolyps |
| **Histologic Features** | Transmural distribution with skip lesions<br>Focal inflammation<br>± noncaseating granulomas, deep fissuring + aphthous ulcerations, strictures<br>Glands intact | Mucosal distribution, continuous disease (no skip lesions)<br>Architectural distortion, gland disruption, crypt abscess<br>Granulomas absent |
| **Radiologic Features** | Cobblestone mucosa<br>Frequent strictures and fistulae<br>AXR: bowel wall thickening "string sign" | Lack of haustra<br>Strictures rare; need to rule out complicating cancer |
| **Complications** | Strictures, fistulae, perianal disease | Toxic megacolon |
| **Colon Cancer Risk** | Increased if >30% of colon involved | Increased except in proctitis |

**Table 14. Extraintestinal Manifestations (EIM) of IBD**

| System | Crohn's Disease | Ulcerative Colitis |
|---|---|---|
| **Dermatologic** | | |
| Erythema nodosum | 15% | 10% |
| Pyoderma gangrenosum | 10% | Less common |
| Perianal skin tags | 75-80% | Rare |
| Oral mucosal lesions | Common | Rare |
| Psoriasis | Statistically associated in 5-10% of those with IBD but not an EIM | |
| Stomatitis | | |
| **Rheumatologic** | | |
| Peripheral arthritis | 15-20% of those with IBD (CD>UC) | |
| Ankylosing spondylitis | 10% of those with IBD (CD>UC) | |
| Sacroiliitis | Occurs equally in CD and UC | |
| **Ocular (~10% of IBD)** | | |
| Uveitis (vision threatening) | | |
| Episcleritis (benign) | 3-4% of IBD patients (CD>UC) | |
| **Hepatobiliary** | | |
| Cholelithiasis | 15-35% of patients with ileal Crohn's | |
| PSC | 1-5% of IBD cases involving colon | |
| Fatty liver | | |
| Gallstones | Pigment stones in CD | |
| **Urologic** | | |
| Calculi | Most common in CD, especially follow ileal resection or extensive terminal ileal disease (oxalate stones) | |
| Ureteric obstruction | | |
| Fistulae | Characteristic of Crohn's | |
| **Others** | | |
| Thromboembolism | | |
| Vasculitis | | |
| Osteoporosis | Increased in CD with/without prior steroids, in UC only after steroids usage | |
| Vitamin deficiencies (B12, Vit ADEK) | | |
| Cardiopulmonary disorders | | |
| Pancreatitis (rare) | | |
| Phlebitis | | |

# Crohn's Disease

## Definition
- chronic transmural inflammatory disorder potentially affecting the entire gut from mouth to perianal region ("gum to bum")

## Epidemiology
- worldwide incidence 3-15 to 10-20/100,000; 135,000 Canadians living with Crohn's
- bimodal: onset before 30 yr, second smaller peak age 60; M=F
- incidence of Crohn's increasing (relative to UC) especially in young females
- more common in Caucasians, Ashkenazi Jews
  - risk in Asians increases with move to Western countries
- smoking incidence in Crohn's patients is higher than general population

## Pathology
- most common location: ileum + right colon
- linear ulcers leading to mucosal islands and "cobblestone" appearance
- granulomas are found in 50% of surgical specimens, 15% of mucosal biopsies

## Clinical Features
- natural history unpredictable; young age, perianal disease, and need for corticosteroids have been associated with poor prognosis, but associations are not strong enough to guide clinical decisions
- most often presents as recurrent episodes of abdominal cramps, non-bloody diarrhea, and weight loss
- ileitis may present with post-prandial pain, vomiting, RLQ mass; mimics acute appendicitis
- extra-intestinal manifestations are more common with colonic involvement
- fistulae, fissures, abscesses are common
- deep fissures with risk of perforation into contiguous viscera (leads to fistulae and abscesses)
- enteric fistulae may communicate with skin, bladder, vagina, and other parts of bowel

## Investigations
- colonoscopy with biopsy to visualize (less often gastroscopy)
- CT/MR enterography to visualize small bowel
- CRP elevated in most new cases, useful to monitor treatment response (especially acutely in UC)
- bacterial cultures, O&P, *C. difficile* toxin to exclude other causes of inflammatory diarrhea

## Management (see Figure 8)

**Effect of Tight Control Management on Crohn's Disease (CALM): A Multi-Centre, Randomized Controlled Phase 3 Trial**
Lancet 2017; 390:2779-2789
**Purpose**: To define the role of incorporating laboratory biomarkers in the management algorithm of active Crohn's disease.
**Study**: Randomized controlled trial.
**Population**: 224 adult patients (22 countries at 74 hospitals) with active Crohn's disease were randomized to intensify treatment based on either laboratory biomarkers (serum C-reactive protein, fecal calprotectin) plus clinical evaluation (Crohn's disease activity index and prednisone use) or treatment based on clinical evaluation alone.
**Outcomes**: Mucosal healing via the absence of deep ulcers.
**Results**: At 2 years, more patients receiving treatment criteria that included laboratory tests had complete mucosal healing (i.e. no ulcers) than the group treated on basis of symptoms alone (46% vs 30%). Admittedly, the end-point of mucosal healing is not a strong clinically relevant result, but other studies have shown that the greater the mucosal ulceration, the more likely are complications, (strictures, fistulas, abscesses, hospitalizations and surgery).
**Conclusions**: This is not definitive data but adds to other evidence showing that the traditional management paradigm needs reversing, so in most patients it is worthwhile aiming for endoscopic healing of Crohn's disease irrespective of symptoms.

**Table 15. Management of Crohn's Disease**

| Management | Notes |
|---|---|
| **Lifestyle/Diet** | Smoking cessation<br>Fluids only during acute exacerbation<br>Enteral diets may aid in remission only for Crohn's ileitis, not colitis<br>No evidence for any non-enteral diet changing the natural history of Crohn's disease, but may affect symptoms<br>Those with extensive small bowel involvement or extensive resection require electrolyte, mineral, and vitamin supplements (vitaminD, $Ca^{2+}$, $Mg^{2+}$, zinc, Fe, $B_{12}$) |
| **Antidiarrheal Agents*** | Loperamide (Imodium®) > diphenoxylate (Lomotil®) > codeine (cheap but addictive)<br>All work by decreasing small bowel motility, used only for symptom relief<br>CAUTION if colitis is severe (risk of precipitating toxic megacolon), therefore avoid during flare-ups |
| **5-ASA**** | Efficacy controversial: Is currently used for mild ileitis<br>Sulfasalazine (Salazopyrin®): 5-ASA bound to sulfapyridine<br>Hydrolysis by intestinal bacteria releases 5-ASA (active component)<br>Dose-dependent efficacy<br>Mesalamine (Pentasa®): coated 5-ASA releases 5-ASA in the ileum and colon when inflammation is mild |
| **Antibiotics** | e.g. metronidazole (20 mg/kg/d, bid or tid dosing) or ciprofloxacin<br>Best described for perianal Crohn's, although characteristically relapse when discontinued |
| **Corticosteroids** | Prednisone: starting dose 40 mg OD for acute exacerbations; IV methylprednisolone if severe<br>No proven role for steroids in maintaining remissions; masks intra-abdominal sepsis |
| **Immunosuppressives** | 6-mercaptopurine (6-MP), azathioprine (Imuran®); methotrexate (used less often)<br>More often used to maintain remission than to treat active inflammation<br>Most commonly used as steroid-sparing agents<br>i.e. to lower risk of relapse as corticosteroids are withdrawn<br>May require >3 mo to have beneficial effect; usually continued for several years<br>May help to heal fistulae, decrease disease activity<br>Increases efficacy of biologicals plus lowers chances of biological dosing efficacy (tolerance) so often given in combination with biologics<br>Side effects: vomiting, pancreatitis, bone marrow suppression, increased risk of malignancy (i.e. lymphoma) |
| **Biologics** | Infliximab IV (Remicade®) or adalimumab SC (Humira®): both = antibody to TNF-α<br>Proven effective for treatment of fistulae and patients with medically refractory CD<br>First-line immunosuppressive therapy with infliximab + azathioprine more effective than using either alone<br>Ustekinumab, monoclonal antibody against P40 subunit of interleukin 12 and 23<br>Vedolizumab, monoclonal antibody directed against integrin α4β7 thereby reducing lymphocyte traffic to gut – now indicated for UC and Crohn's |
| **Surgical/ Experimental** | Surgical treatment (see General Surgery, GS33)<br>Surgery generally reserved for complications such as fistulae, obstruction, abscess, perforation, bleeding, and for medically refractory disease<br>If <50% or <200 cm of functional small intestine, risk of short bowel syndrome<br>At least 50% clinical recurrence within 5 yr; 85% within 15 yr; endoscopic recurrence rate even higher<br>40% likelihood of second bowel resection, 30% likelihood of third bowel resection<br>Complications of ileal resection<br><100 cm resected → watery diarrhea or cholorrhea (impaired bile salt absorption)<br>Treatment: cholestyramine or anti-diarrheals e.g. loperamide<br>>100 cm resected → steatorrhea (reduced mucosal surface area, bile salt deficiency)<br>Treatment: fat restriction, medium chain triglycerides |

*Cholestyramine: a bile-salt binding resin; for watery diarrhea with <100 cm of terminal ileum diseased or resected; however, non-specific anti-diarrheals are more convenient and often more potent
** 5-ASA use in Crohn's is controversial; however, initial trial for mild ilelitis only is warranted (induction and maintenance if clinical response)

**Traditional Medical Management of Crohn's**

| | Induction of Remission | Maintenance |
|---|---|---|
| 5-ASA* | ? | ? |
| Steroids | + | |
| Immunosuppressive | + | + |
| Antibiotics | + | |
| MTX | + | + |
| Infliximab | + | + |

*5-ASA use in Crohn's is controversial. However, initial trial for mild ilelitis only is warranted (induction and maintenance if clinical response)

**Note:** Starting with immunosupressives plus immunomodulators ("top-down approach") increasingly being used (Lancet 2008;371;660-67). Combination of azathioprine and infliximab has the highest remission rate yet described with medical treatment (NEJM 2010;362;1383-95). Characteristically more than 1 yr between onset of symptoms and diagnosis of Crohn's disease.

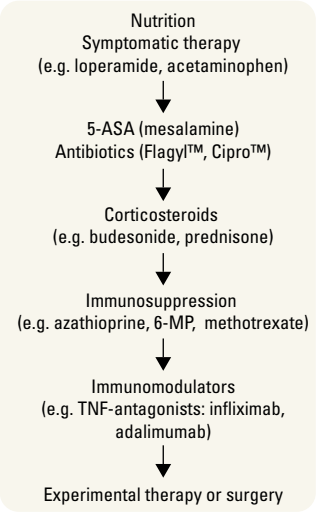



**Figure 8. Traditional graded approach to induction therapy in Crohn's disease**
Note: immunosuppressants and immunomodulators are increasingly used initially ("top-down management strategy")

## Prognosis

- highly variable course
- 10% disabled by the disease eventually, spontaneous remission also described
- increased mortality, especially with more proximal disease, greatest in the first 4-5 yr
- complications include
  - intestinal obstruction/perforation
  - fistula formation
  - malignancy (lower risk compared to UC)
- surveillance colonoscopy same as ulcerative colitis (see Ulcerative Colitis) if more than 1/3 of colon involved

# Ulcerative Colitis

## Definition

- inflammatory disease affecting colonic mucosa anywhere from rectum (always involved) to cecum

## Epidemiology

- worldwide incidence 3-15 to 10-20/100,000; 120,000 Canadians living with UC (less common than Crohn's)
- 2/3 onset by age 30 (with second peak after 50); M=F
- small hereditary contribution (15% of cases have 1st degree relative with disease)
- risk is less in smokers
- inflammation limited to rectum or left colon is more common than pancolitis

## Pathology
- disease can involve any portion of lower bowel ranging from rectum only (proctitis) to entire colon (pancolitis)
- inflammation is diffuse, continuous and confined to mucosa

## Clinical Features
- rectal bleeding is the hallmark feature; diarrhea present if more than the rectum is involved
  - can also have abdominal cramps/pain, especially with defecation
- severity of colonic inflammation correlates with symptoms (stool volume, amount of blood in stool)
- tenesmus, urgency, incontinence
- systemic symptoms: fever, anorexia, weight loss, fatigue in severe cases
- extra-intestinal manifestations (see Table 14, G23)
- characteristic exacerbations and remissions; 5% of cases are fulminant

In UC, non-bloody diarrhea is frequently the initial presentation; eventually progressing to bloody diarrhea

## Investigations
- sigmoidoscopy with mucosal biopsy (to exclude self-limited colitis) without bowel prep often sufficient for diagnosis
- colonoscopy helpful to determine extent of disease; contraindicated in severe exacerbation
- CT colonography (formerly barium enema) if colonoscopy cannot be done; contraindicated in severe disease
- stool culture, microscopy, *C. difficile* toxin assay necessary to exclude infection
- no single confirmatory test

**Medical Management of Ulcerative Colitis**

| | Induction of Remission | Maintenance |
|---|---|---|
| 5-ASA | + | + |
| Steroids | + | |
| Immunosuppressive | ± | + |

## Treatment
- mainstays of treatment: 5-ASA (mesalamine) derivatives (only in mild to moderate disease) and corticosteroids, with azathioprine used in steroid-dependent or resistant cases
- diet of little value in decreasing inflammation but may alleviate symptoms
- anti-diarrheal medications generally not indicated in UC
  - 5-ASA
    - topical (suppository or enema): effective for distal disease (rectum to splenic flexure) if inflammation is mild, preferable to corticosteroids
    - oral: effective for mild to moderate, but not severe colitis (e.g. sulfasalazine 3-4 g/d, mesalamine 4 g/d)
    - commonly used in maintaining remission (decreases yearly relapse rate from 60% to 15%)
    - may decrease rate of colorectal cancer
- corticosteroids
  - to remit acute disease, especially if severe or first attack; may need maximum dose IV steroids initially (e.g. methylprednisolone 30 mg IV q12h)
  - limited role as maintenance therapy for mild to moderate disease
  - use suppositories (predominantly available in compound pharmacies) for proctitis
  - use enemas and topical steroids (e.g. hydrocortisone foam, budesonide enemas) for inflammation distal to splenic flexure
- immunosuppressants (steroid-sparing)
  - in hospitalized patients with severe UC – add IV infliximab if no response to IV methylprednisolone within 3 d; then consider colectomy if inadequate response
  - biologics (infliximab, adalimumab, golimumab, vedolizumab, tofacitinib) can also be used for outpatients with moderate-severe disease, particularly those that are steroid-unresponsive or steroid-dependent, some evidence that they are best used early in course of disease
  - azathioprine and 6-mercaptopurine: too slow to rapidly resolve acute relapse
    - most commonly used to maintain remission as corticosteroids withdrawn
    - given with biologics: increase efficacy of infliximab and decrease likelihood of developing tolerance to infliximab (~10% chance/yr)
- surgical treatment curative
  - aim for cure with colectomy; bowel continuity can be restored with ileal pouch-anal anastamosis (IPAA)
  - indications: failure of adequate medical therapy, toxic megacolon, uncontrollable bleeding, pre-cancerous changes detected either by endoscopy or endoscopic biopsies (dysplasia), inability to taper corticosteroids, overt malignancy

**When Considering Complications of IBD, Think:**

**ULCERATIVE COLITIS**
**U**rinary calculi
**L**iver problems
**C**holelithiasis
**E**pithelial problems
**R**etardation of growth/sexual maturation
**A**rthralgias
**T**hrombophlebitis
**I**atrogenic complications
**V**itamin deficiencies
**E**yes
**C**olorectal cancer
**O**bstruction
**L**eakage (perforation)
**I**ron deficiency
**T**oxic megacolon
**I**nanition (wasting)
**S**trictures

## Complications
- similar to CD, except:
  - more liver problems (especially PSC in men)
  - greater risk of colorectal cancer
    - risk increases with duration and extent of disease (5% at 10 yr, 15% at 20 yr for pancolitis; overall relative risk is 8%)
    - risk also increases with active mucosal inflammation and sclerosing cholangitis
    - thus, regular colonoscopy and biopsy in pancolitis of ≥8 yr is indicated
  - toxic megacolon (transverse colon diameter >6 cm on abdominal x-ray) with immediate danger of perforation (see General Surgery, GS42)

### Prognosis
- chronic relapsing pattern in most patients
- 10-15% chronic continuous pattern
- >1 attack in almost all patients
- more colonic involvement in the 1st yr correlates with increased severity of attacks and increased colectomy rate
  - colectomy rate = 1% for all patients after the 1st yr; 20-25% eventually undergo colectomy
- normal life expectancy
- if proctitis only, usually benign course, lifetime risk of extension is 15%
- stool calprotectin increasingly recognized as a marker of bowel mucosal inflammation, reported especially to be useful in monitoring the activity of inflammatory bowel disease, but accuracy is still controversial

## Irritable Bowel Syndrome



### Definition
- a form of functional bowel disease; more than just a label for GI symptoms unexplained after normal investigations

### Epidemiology
- 11% worldwide prevalence
- onset of symptoms usually in young adulthood
- F>M

### Clinical Features
- Rome IV Criteria are used for diagnosis
- diagnosis is based chiefly on history; no specific diagnostic test available

### Pathophysiology
- associated with either abnormal perception of intestinal activity or abnormal intestinal motility
- abnormal motility: multiple abnormalities described; unclear if associations or if causative
- psychological: stress may increase IBS symptoms but probably does not cause IBS
- 4 main types of IBS
  - IBS-D: IBS with predominant diarrhea
  - IBS-C: IBS with predominant constipation
  - IBS-M: IBS-mixed with both diarrhea and constipation (each >25% of all abnormal bowel movements)
  - IBS untyped: insufficient abnormality in stool consistency to meet other types

### Diagnosis

**Table 16. Rome IV Criteria for Diagnosing Irritable Bowel Syndrome**

| **IBS Rome IV Criteria** | |
|---|---|
| Recurrent abdominal pain for more than 6 mo, of at least 1/d/wk in the last 3 mo, associated with 2 or more of the following:<br>1. Related to defecation<br>2. Associated with a change in frequency of stool<br>3. Associated with a change in form (appearance) of stool | |
| Symptom onset at least 6 mo before diagnosis and criteria present during the last 3 mo | |
| The following are supportive, but not essential to the diagnosis:<br>Abnormal stool frequency (>3/d or <3/wk)<br>Abnormal stool form (lumpy/hard/loose/watery) >1/4 of defecations<br>Abnormal stool passage (straining, urgency, feeling of incomplete evacuation) >1/4 of defecations<br>Passage of mucus >1/4 of defecations<br>Bloating | |
| **Diagnosis of IBS Less Likely in Presence of "Red Flag" Features** | |
| Weight loss | Anemia |
| Fever | Blood or pus in stool |
| Nocturnal defecation | Abnormal gross findings on flexible sigmoidoscopy |
| **Normal Physical Exam** | |

### Investigations
- if history consistent with Rome IV criteria, no alarm symptoms, and no family history of IBD or colorectal cancer, limited investigations required
- aim is to rule out diseases which mimic IBS, particularly celiac disease and IBD
- investigations can be limited to CBC, inflammatory markers (ESR, CRP) and celiac serology
- if available, fecal calprotectin is likely more reliable test to rule out IBD
- consider TSH, stool cultures depending on clinical circumstances
- consider colonoscopy (e.g. if alarming features present, family history of IBD or age >50)



**IBS Mimickers**
- Enteric infections e.g. *Giardia*
- Lactose intolerance/other disaccharidase deficiency
- Crohn's disease
- Celiac sprue
- Drug-induced diarrhea
- Diet-induced (excess tea, coffee, colas)

### Treatment
- education: reassurance, explanation, support, aim for realistic goals
- relaxation therapy, biofeedback, hypnosis, stress reduction, probably exercise
- dietary: low FODMAP (Fermentable Oligo-, Di-, Monosaccharides And Polyols) diet for pain, bloating gas, irregular bowel movements

- no therapeutic agent consistently effective, pain most difficult to control, no drug changes natural history so the drug should be "wanted, since it is not needed"
- symptom-guided treatment
  - pain predominant
    - antispasmodic medication before meals (e.g. hyoscine, pinaverium, trimebutine - low level evidence)
    - tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI - moderate level of evidence)
  - IBS-D
    - increase fibre (bran or psyllium) to increase stool consistency but may worsen abdominal gas (controversial)
    - gluten avoidance (gluten shown to alter barrier)
    - loperamide (Imodium®)
    - diphenoxylate (Lomotil®)
    - cholestyramine
    - eluxadoline
    - rifaxamin
  - IBS-C
    - increase fibre in diet
    - linaclotide
    - osmotic or other laxatives (help more with the constipation than the pain)

### Prognosis
- 80% improve over time
- most have intermittent episodes
- normal life expectancy

**Rifaximin Therapy for Patients with Irritable Bowel Syndrome Without Constipation**
NEJM 2011;364:22-32
**Purpose**: Previous evidence suggests that gut flora may play an important role in the pathophysiology of IBS. This study evaluated rifaximin, a minimally absorbed antibiotic, in treating IBS without constipation.
**Methods**: Two phase 3, double-blind, placebo-controlled trials (TARGET 1 and TARGET 2). 1260 patients who had IBS without constipation were randomly assigned to rifaximin (550 mg dose) or placebo, 3 times daily for 2 wk, with a follow-up of 10 wk. The primary endpoint was adequate self-reported relief of global IBS symptoms.
**Results**: Significantly more patients in the rifaximin group had adequate self-reported relief of global IBS symptoms compared to the placebo group during the first 4 wk after treatment (40.8% vs. 31.2% respectively). Also, more patients in the rifaximin group had adequate relief of bloating compared to the placebo group (39.5% vs. 28.7% respectively).
**Conclusions**: Rifaximin therapy for 2 wk provided significant relief of symptoms, bloating, abdominal pain, and stool consistency associated with IBS without constipation.

# Constipation

### Definition
- passage of infrequent/hard stools and/or difficult stool evacuation (ex. straining, sensation of anorectal blockage)

### Epidemiology
- increasing prevalence with age; F>M
- rare in Africa and India where stool weight is 3-4x greater than in Western countries

### Risk Factors
- female sex
- older age

**Causes of Constipation**

**DOPED**
**D**rugs
**O**bstruction
**P**ain
**E**ndocrine dysfunction
**D**epression

### Etiology
- most common: functional, idiopathic attributed to colon dysmotility but this is difficult to measure
- organic causes: likely only if there are symptoms other than constipation
  - medication side effects (narcotics, antidepressants) are the most common
  - intestinal obstruction, left sided colon cancer (consider in older patients), and fecal impaction
  - metabolic
    - DM
    - hypothyroidism
    - hypercalcemia, hypokalemia, uremia
  - neurological
    - intestinal pseudo-obstruction
    - Parkinson's disease
    - MS
  - collagen vascular disease (e.g. scleroderma)
  - painful anal conditions (e.g. fissures)

### Clinical Feature
- overlaps with IBS
- stool firm, difficult to expel, passed with straining, abdominal pain relieved by defecation, flatulence, overflow diarrhea, tenesmus, abdominal distension, infrequent BMs (<3/wk)

### Investigations
- underlying disease rarely found if constipation is the only presenting symptom
  - only test indicated in this situation is a CBC (2013 recommendation of American Gastroenterology Association), but also consider TSH, calcium, and glucose, X-ray of abdomen
- colon visualization (colonoscopy, CT colonography) if concomitant symptoms such as rectal bleeding, weight loss, anemia or age above 50
- if refractory to treatment, consider classification based on colon transit time; can measure colonic transit time with radio-opaque markers that are ingested and followed with a series of plain film abdominal x-rays (normal: 70 h)
  1. normal = misperception of normal defecation (IBS)
  2. prolonged throughout = "colonic inertia" (infrequent bowel movements with gas/bloating, tends to occur in youth)
  3. outlet obstruction = inability to coordinate pelvic floor muscles to empty rectum, straining, stool in rectum on digital exam, tends to occur in old age
- combination of 1 and 3 common

### Treatment (in order of Increasing Potency)

- dietary fibre
  - useful if mild or moderate constipation, but not if severe
  - aim for 30 g daily, increase dose slowly
- surface-acting (soften and lubricate)
  - docusate salts (likely limited efficacy based on evidence), mineral oils
- osmotic agents (effective in 2-3 d)
  - polyethylene glycol 3350, lactulose, sorbitol, magnesium salts (e.g. magnesium hydroxide, i.e. milk of magnesia), lactitol (β-galactosido-sorbitol)
- cathartics/stimulants (effective in 24 h)
  - senna, bisacodyl
- enemas and suppositories (e.g. saline enema, phosphate enema, glycerin suppository, bisacodyl suppository)
- prokinetic agents (prucalopride)
- linaclotide (secretagogue, increases water secretion into the intestinal lumen)

# Upper Gastrointestinal Bleeding

### Definition

- bleeding proximal to the ligament of Treitz, see *Gastrointestinal Tract*, G2 (75% of GI bleeds)
  - ligament of Treitz: suspensory ligament where fourth portion of the duodenum transitions to jejunum

### Etiology

- above the GE junction
  - epistaxis
  - esophageal varices (10-30%)
  - esophagitis
  - esophageal cancer
  - Mallory-Weiss tear (10%)
- stomach
  - gastric ulcer (20%) (see *Peptic Ulcer Disease*, G11)
  - erosive gastritis (e.g. from EtOH or post-surgery) (20%)
  - gastric cancer
  - gastric antral vascular ectasia (rare, associated with cirrhosis and connective tissue disease)
  - Dieulafoy's lesion (very rare)
- duodenum
  - ulcer in bulb (25%)
  - aortoenteric fistula: usually only if previous aortic graft (see sidebar)
- coagulopathy (drugs, renal disease, liver disease)
- vascular malformation (Dieulafoy's lesion, arteriovenous malformation)

### Clinical Features

- in order of decreasing severity of the bleed: hematochezia (brisk upper GI bleed) > hematemesis > coffee ground emesis > melena > occult blood in stool

### Treatment

- stabilize patient (1-2 large bore IVs, IV fluids, monitor)
- send blood for CBC, cross and type, platelets, PT, PTT, electrolytes, BUN, Cr, LFTs
- keep NPO
- consider NG tube to determine upper vs. lower GI bleeding in some cases
- IV PPI: decrease risk of rebleed if endoscopic predictors of rebleeding seen (see prognosis section)
  - given to stabilize clot, not to accelerate ulcer healing
  - if given before endoscopy, decreases need for endoscopic therapeutic intervention
- for variceal bleeds, octreotide 50 μg loading dose followed by constant infusion of 50 μg/h and antibiotics for those with cirrhosis (reduces risk of infections)
- consider IV erythromycin (or metoclopramide) to accelerate gastric emptying prior to gastroscopy to remove clots from stomach
- endoscopy (OGD): establish bleeding site + treat lesion
  - if bleeding peptic ulcer: most commonly used method of controlling bleeding is injection of epinephrine around bleeding point + thermal hemostasis (bipolar electrocoagulation or heater probe); less often thermal hemostasis may be used alone, but injection alone not recommended
  - endoclips
  - hemospray

### Prognosis

- 80% stop spontaneously
- peptic ulcer bleeding: low mortality (2%) unless rebleeding occurs (25% of patients, 10% mortality)
- endoscopic predictors of rebleeding (Forrest classification): spurt or ooze, visible vessel, fibrin clot
- can send home if clinically stable, bleed is minor, no comorbidities, endoscopy shows clean ulcer with no high risk predictors of rebleeding
- H2-antagonists should not be used since they impact minimally on rebleeding rates and need for surgery
- esophageal varices have a high rebleeding rate (55%) and mortality (29%)



Always ask about NSAID/Aspirin® or anticoagulant therapy in GI bleed



**Aortoenteric Fistula** is a rare and lethal cause of GI bleed, most common in patients with a history of aortic graft surgery. Therefore, perform emergency endoscopy if suspected, emergency surgery if diagnosed
Note: The window of opportunity is narrow. Suspect if history of aortic graft, abdominal pain associated with bleeding



**Transfusion Strategies for Acute Upper Gastrointestinal Bleeding**
NEJM 2013;368:11-21
**Study**: Prospective, unblinded, RCT, follow-up up to 45 d.
**Populations**: 921 patients with hematemesis, bloody nasogastric aspirate, melena, or both. Exclusion criteria included massive bleed, ACS, stroke/TIA or transfusion within previous 90 d; recent trauma/surgery; lower GI bleed.
**Intervention**: Patients randomized to restrictive (<70 g/L) or liberal (<90 g/L) transfusion.
**Outcome**: Mortality, further bleeding, adverse events.
**Results**: Fewer patients in the restrictive group required transfusion (51% vs. 15%; p<0.001). The hazard ratio for death for restrictive compared to liberal transfusion was 0.55; 95% CI 0.33-0.92; p=0.02. Further bleeding occurred in 10% vs. 16% (p=0.01) of patients, while adverse effects occurred in 40% vs. 48% (p=0.02) of patients in the restrictive and liberal strategies, respectively. The restrictive strategy had a better survival rate in patients with bleeding associated with cirrhosis Child-Pugh class A or B (HR: 0.30; 95% CI 0.11-0.85), but not in cirrhosis Child-Pugh class C (HR: 1.04; 95% CI 0.45-2.37) or a peptic ulcer (HR: 0.70; 95% CI 0.26-1.25).
**Conclusions**: Transfusing patients with an acute upper GI bleed at hemoglobin of <70 g/L rather than 90 g/L is associated with fewer transfusions, better survival, and fewer adverse events.



**Forrest Prognostic Classification of Bleeding Peptic Ulcers**

| Forrest Class | Type of Lesion | Risk of Rebleed (%) |
|---|---|---|
| I | Arterial bleeding (oozing/spurting) | 55-100 |
| IIa | Visible vessel | 43 |
| IIb | Sentinel clot | 22 |
| IIc | Hematin covered flat spot | 10 |
| III | No stigmata of hemorrhage | 5 |

*Lancet* 1974;2:394-397

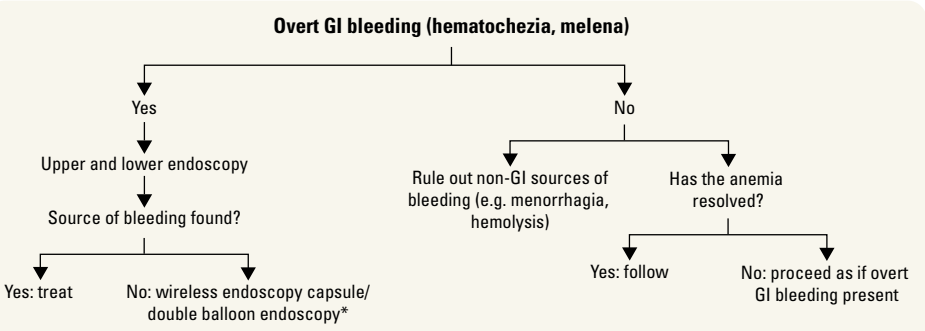



**Figure 9. Approach to iron deficiency anemia**

# Esophageal Varices

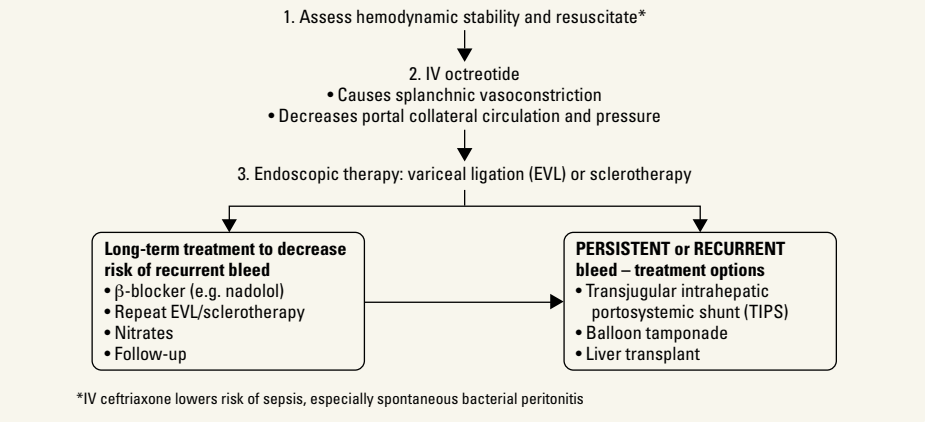
### Etiology
- almost always due to portal hypertension

### Clinical Features
- characteristically massive upper GI bleeding

### Prognosis
- risk of bleeding: 30% in 1st yr
- risk of rebleeding: 50-70% (20% mortality at 6 wk)

### Investigations
- endoscopy

### Management






If varices isolated to stomach, think of splenic vein thrombosis



Gastric varices best treated by endoscopic injection of cyanoacetate ("crazy glue")

**Figure 10. Management of bleeding esophageal varices**

# Mallory-Weiss Tear

### Definition
- longitudinal laceration in gastric mucosa on lesser curvature near GE junction (20% straddle junction, 5% in distal esophagus)

### Etiology
- due to rapid increases in gastric pressure from retching/vomiting against a closed glottis
- hiatus hernia usually present

### Clinical Features
- hematemesis ± melena, classically following an episode of retching without blood
- can lead to fatal hematemesis

### Management
- 90% stop spontaneously
- if persistent: endoscopy with epinephrine injection ± clips or surgical repair

# Lower Gastrointestinal Bleeding

## Definition
- bleed distal to ligament of Treitz

## Etiology
- if blood per rectum with hemodynamic instability, rule out upper GI source
- diverticular (60% from right colon)
- vascular
  - angiodysplasia (small vascular malformations of the gut)
  - anorectal (hemorrhoids, fissures)
- neoplasm
  - cancer
  - polyps
- inflammation
  - colitis (ulcerative, infectious, radiation, ischemic)
- post-polypectomy

**Lower GI Bleed**

**CHAND**
**C**olitis (radiation, infectious, ischemic, IBD [UC > CD])
**H**emorrhoids/fissure
**A**ngiodysplasia
**N**eoplastic
**D**iverticular disease

## Clinical Features
- hematochezia
- anemia
- occult blood in stool
- occasionally melena due to slow small bowel or right-colonic course

## Treatment
- treat underlying cause

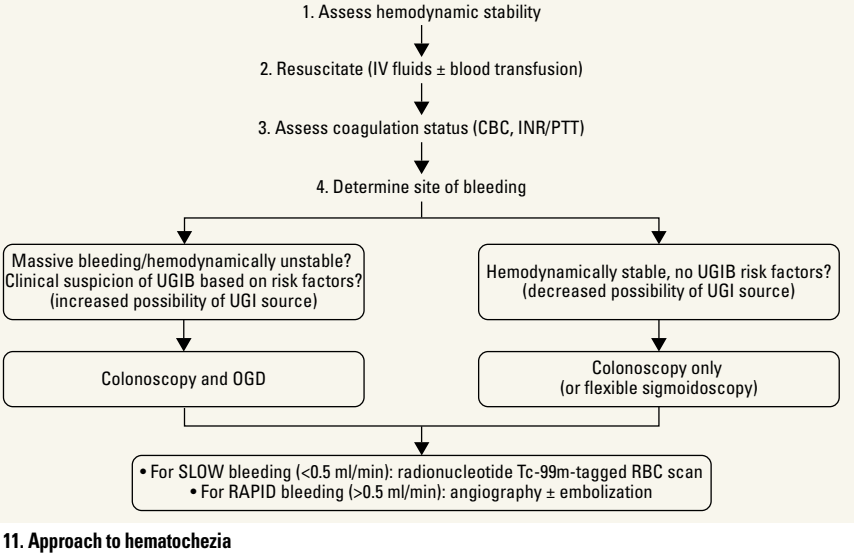



**Figure 11. Approach to hematochezia**

Always exclude upper GI lesion before localizing the site of the bleeding to the lower GI tract

# Colorectal Carcinoma

- see General Surgery, GS39

# Colorectal Polyps

- see General Surgery, GS38

# Familial Colon Cancer Syndromes

- see General Surgery, GS38

# Benign Anorectal Disease

- see General Surgery, GS44

# Liver

## Investigations of Hepatobiliary Disease

### A. Tests of Liver Function

**Table 17. Liver Function Tests**

| Test | What Do Levels Correlate With? | Increased by | How to Interpret |
|---|---|---|---|
| **Prothrombin Time (PT or INR)** | Hepatic protein synthesis<br>All coagulation factors except VIII | Hepatocellular dysfunction<br>Vitamin K deficiency (due to malnutrition, malabsorption, etc.) | PT/INR will promptly correct if vitamin K is administered, so increased PT/INR in absence of vitamin K deficiency is a reliable marker of hepatocellular dysfunction |
| **Serum Albumin** | Hepatic protein synthesis (and other causes listed in next column) | Hepatocellular dysfunction<br>Malnutrition<br>Renal or GI losses<br>Significant inflammation<br>Malignancy | Rule out potential causes other than hepatocellular dysfunction |
| **Serum Direct Bilirubin*** | Hepatic excretion from hepatocyte to biliary system | Liver dysfunction | Conjugation is preserved even in end stage liver failure, thus increased direct bilirubin indicates liver dysfunction |

*Serum Bilirubin
- canaliculus breakdown product of hemoglobin; metabolized in the reticuloendothelial system of liver, transported through biliary system, excreted via gut
- direct bilirubin = conjugated; indirect = unconjugated bilirubin

All clotting factors except factor VIII and von Willebrand factor are exclusively synthesized in the liver. Factor VIII is also produced in the endothelium. In cirrhosis, risk of bleeding does not correlate closely with elevations in INR/PTT since so many of the proteins in the coagulation cascade are affected

### B. Tests of Liver Injury
- disproportionately increased AST or ALT = hepatocellular damage
  - ALT more specific to liver; AST from multiple sources (especially muscle)
  - elevation of both highly suggestive of liver injury
  - most common cause of elevated ALT is fatty liver
- disproportionately increased ALP (and GGT) = cholestasis (stasis of bile flow)
  - if ALP is elevated alone, rule out bone disease by fractionating ALP and/or checking GGT
  - if ALP elevation out of proportion to ALT/AST elevation, consider:
    1. obstruction of common bile duct (e.g. extraluminal = pancreatic cancer, lymphoma; intraluminal = stones, cholangiocarcinoma, sclerosing cholangitis, helminths)
    2. destruction of microscopic ducts (e.g. PBC)
    3. bile acid transporter defects (e.g. drugs, intrahepatic cholestasis of pregnancy)
    4. infiltration of the liver (e.g. liver metastases, lymphoma, granulomas, amyloid)

ALT > AST = most causes of hepatitis
AST > ALT = alcoholic liver disease or other causes of hepatitis (i.e. non-alcoholic liver disease) that have progressed to advanced cirrhosis

## Acute Viral Hepatitis (General)

### Definition
- viral hepatitis lasting <6 mo

### Clinical Features
- most are subclinical
- flu-like prodrome may precede jaundice by 1-2 wk
  - nausea/vomiting, anorexia, headaches, fatigue, myalgia, low-grade fever, arthralgia, and urticaria (especially HBV)
- only some progress to icteric (clinical jaundice) phase, lasting days to weeks
  - pale stools and dark urine 1-5 d prior to icteric phase
  - hepatomegaly and RUQ pain
  - splenomegaly and cervical lymphadenopathy (10-20% of cases)

**Serum Transaminases >1000 due to**
- Viral hepatitis
- Drugs/toxins
- Autoimmune hepatitis
- Hepatic ischemia
- Less often, common bile duct stone

**Alcoholic hepatitis**: history of recent alcohol, RUQ abdominal pain, AST/ALT>2, AST usually <300, low grade fever, mildly elevated WBC

### Investigations
- AST and ALT (>10-20x normal in hepatocellular necrosis)
- ALP minimally elevated
- viral serology, particularly the IgM antibody directed to the virus

**Major Sources of ALP**
- Hepatobiliary tree
- Bone
- Placenta

### Treatment
- supportive (hydration, diet)
- usually resolves spontaneously, but if severe HBV infection, treatment with entecavir should be considered; in anicteric hepatitis C, anti-viral treatment should be considered (see *Hepatitis C Virus*, G33)
- indications for hospitalization: encephalopathy, coagulopathy, severe vomiting, hypoglycemia

**DDx for Hepatitis**
- Viral infection
- Alcohol
- Drugs
- Immune-mediated
- Toxins

### Prognosis
- poor prognostic indicators: comorbidities, persistently high bilirubin (>340 mmol; 20 mg/dL), increased INR, decreased albumin, hypoglycemia

### Complications
- cholestasis (most commonly associated with HAV infection)
- hepatocellular necrosis: AST, ALT >10-20x normal, ALP and bilirubin minimally increased, increased cholestasis

## Hepatitis A Virus

- RNA virus
- fecal-oral transmission; incubation period 4-6 wk
- diagnosed by elevated transaminases, positive anti-HAV IgM
- in children: characteristically asymptomatic
- in adults: fatigue, nausea, arthralgia, fever, jaundice, hepatomegaly
- can cause acute liver failure and subsequent death (<1-5%)
- can relapse (rarely), but never becomes chronic
- treatment is supportive (no specific treatments available, disease is often self-limiting)

## Hepatitis B Virus

**Table 18. Hepatitis B Serology**

| | HBsAg | Anti-HBs | HBeAg | Anti-HBe | Anti-HBc | Liver Enzymes |
|---|---|---|---|---|---|---|
| **Acute HBV** | + | – | + | – | IgM | |
| **Chronic** (e-Ag positive) HBV (generally high HBV DNA) | + | – | + | – | IgG | ALT, AST may or may not be elevated |
| **Chronic** (e-Ag negative) HBV (generally low HBV DNA) | + | – | – | + | IgG | ALT, AST may or may not be normal |
| **Resolved Infection** | – | ± | – | ± | IgG | |
| **Immunization** | – | + | – | – | – | |

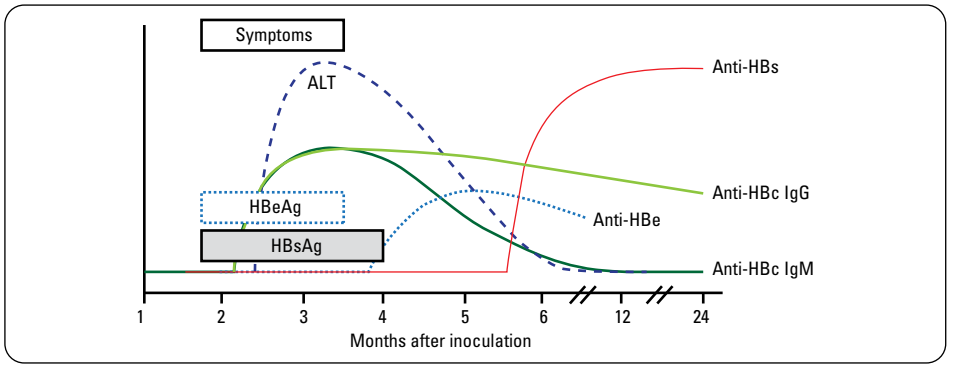



**Figure 12. Time course of acute hepatitis B infection**

### Epidemiology
- 4 phases of chronic hepatitis B: not all carriers will go through all 4 phases, but all carriers will have positive HBsAg
  1. **immune tolerance**: extremely high HBV-DNA (>20,000 IU/mL), HBeAg positive, but normal ALT/AST; due to little immune control and minimal immune-mediated liver damage; characteristic of perinatal infection (or 'incubation period' in adult with newly-acquired HBV)
  2. **immune clearance** (or immunoactive): HBV-DNA levels (>20,000 IU/mL), HBeAg positive; due to immune attack on the virus and immune-mediated liver damage; characterized by progressive disease without treatment and increasing liver fibrosis (sometimes progressing to cirrhosis and/or hepatocellular carcinoma); likely to benefit from treatment
  3. **inactive carrier** (immune control): lower HBV-DNA (<2000 IU/mL), HBeAg negative, anti-HBe positive, ALT/AST normal; due to immune control without immune-mediated liver damage; risk of reactivation to phase 2 (clinically resembles acute hepatitis B), especially with immunosuppression e.g. corticosteroids or chemotherapy
  4. **HBeAg-negative chronic hepatitis** (immune escape) ("core or precore mutant"): elevated HBV-DNA (>2000 IU/mL), HBeAg negative because of pre-core or core promoter gene mutation, anti-HBe positive, ALT/AST high; characterized by progressive disease without treatment and increasing liver fibrosis (sometimes progressing to cirrhosis and/or hepatocellular carcinoma); likely to benefit from treatment

**Causes of Elevated Serum Transaminases in Chronic Hepatitis B**
- Ongoing immune-mediated liver injury without immune control of HBV (HBeAg positive)
- Immune escape (anti-HBe positive)
- Reactivation, seroconversion (conversion from anti-HBe to HBeAg)
- Hepatitis D
- Heptocellular carcinoma
- Other liver insult (fatty liver, alcohol, drugs, hepatitis A)

**Risk Factors for Progression**
- EtOH
- HIV coinfection
- Old age at diagnosis

In acute hepatitis B, HDV coinfection increases severity of hepatitis but does not increase risk of progression to chronic hepatitis. However in the context of chronic hepatitis B, superinfection with HDV increases progression to cirrhosis

Without treatment, 8-20% of those with ongoing immunoactive chronic hepatitis can develop cirrhosis within 5 yr. In contrast, those in the immune tolerant phase (with extremely high HBV-DNA levels) are at minimal risk for liver fibrosis as they do not have immune-mediated liver injury

Risk of hepatocellular carcinoma in HBV increases with increasing age, which is likely a surrogate for increasing liver fibrosis/cirrhosis, and serum HBV-DNA
Risk of hepatocellular carcinoma in HCV increases only after cirrhosis develops

HCV (and HBV) treatment lowers the risk of hepatocellular carcinoma

**Risk Factors for Contracting Hepatitis B**
- Infants born to a hepatitis B-infected parent (maternal or paternal)
- Unprotected sexual intercourse (especially if multiple partners)
- Needle sharing (e.g. injection drug users)
- Travel to endemic regions
- Exposure to human blood, semen, and other bodily fluids

**Clinical Features of Hepatitis B**
- Many patients are asymptomatic, both in the acute and chronic phases
- Acute hepatitis can manifest as jaundice, nausea, arthritis, constitutional symptoms
- Patients with chronic hepatitis can be asymptomatic, experience exacerbations, develop extrahepatic complications (e.g. glomerular disease), or develop cirrhosis

### Treatment
- counselling: 40% of men and 10% of women with perinatal infection without treatment will die from HBV-related complications
- prolonged immune-mediated damage leads to higher risk of liver fibrosis
- hepatocellular carcinoma screening with ultrasound q6mo, especially if high serum HBV-DNA levels, cirrhosis, men, (age >40 in Asian men, >50 in Asian women, and >20 in African descent)
- consider pharmacological therapy if:
  1. HBeAg positive + HBV-DNA >20,000 IU/mL + elevated ALT; or
  2. HBeAg negative + HBV-DNA >2000 IU/mL + elevated ALT ± stage ≥2 fibrosis on liver biopsy
  3. treat to prevent flare when placed on immunosuppressive therapy such as prednisone, chemotherapy, biologics, etc.
- treatment goal: reduce serum HBV-DNA to undetectable level
- treatment options: interferon, tenofovir, entecavir, lamivudine
- vaccinate against HAV if serology negative (to prevent further liver damage)
- follow blood and sexual precautions

## Hepatitis D Virus

- defective RNA virus requiring HBsAg for entry into hepatocyte, therefore infects only patients with HBV; causes more aggressive disease than hepatitis B virus alone
- coinfection: acquire HDV and HBV at the same time
- HDV can present as Acute Liver Failure and/or accelerate progression to cirrhosis
- treatment: low-dose interferon (20% response) and liver transplant for end-stage disease

## Hepatitis C Virus

- RNA virus (7 genotypes; genotype 1 is most common in North America)
- blood-borne transmission; sexual transmission is "inefficient"
- major risk factor: injection drug use
- other risk factors: blood transfusion received before 1992 (or received in developing world), tattoos, intranasal cocaine use
- clinical manifestation develops 6-8 wk after exposure
  - symptoms mild and vague (fatigue, malaise, nausea) therefore not commonly diagnosed in acute stage

### Diagnosis
- suspected on basis of elevated ALT/AST and positive serum anti-HCV
- diagnosis established by detectable HCV-RNA in serum
- virus genotype correlates with response to treatment but not prognosis
  - serum HCV-RNA inversely correlates with response to treatment
- normal transaminases can have underlying cirrhosis on biopsy, but otherwise excellent prognosis

### Treatment
- blood-borne precautions; vaccinate for hepatitis A and B if serology negative; avoid alcohol
- clearest indication for treatment is in subgroups likely to develop clinically significant liver disease, i.e. persistently elevated transaminases, liver biopsy showing fibrosis/cirrhosis, and at least moderately severe necrosis/inflammation
  - now that safe, effective cure is available, the risk/benefit ratio favours treating everyone with chronic hepatitis C
- treatment depends partly on genotype; length of treatment depends on degree of fibrosis, level of serum HCV-RNA, comorbidities, and previous treatment
- oral interferon-free regimens (for all genotypes) (e.g. sofosbuvir/ledipasvir, ombitasvir/paritaprevir/ritonavir+dasabuvir, or elbasvir/grazoprevir and sofosbuvir/velpatasvir) are now the standard of care with >90% success rate without significant side-effects including those who failed previous interferon-based treatment

### Prognosis
- 80% of acute hepatitis C become chronic (of these 20% evolve to cirrhosis)
- risk of hepatocellular carcinoma increases if cirrhotic
- can cause cryoglobulinemia; associated with membranoproliferative glomerulonephritis, lymph



**DDx for Hepatomegaly**
- Congestive (right heart failure, Budd-Chiari syndrome)
- Infiltrative
  - Malignant (primary, secondary, lymphoproliferative, leukemia)
  - Benign (fatty liver, cysts, hemochromatosis, extramedullary hematopoiesis, amyloid)
- Proliferative
  - Infectious (viral, tuberculosis, abscess, echinococcus)
  - Inflammatory (granulomas [sarcoid], histiocytosis X)



**From Description to Cure in One Generation**
Ledipasvir and Sofosbuvir for Untreated HCV Genotype 1 Infection
NEJM 2014;370:1889-1898
If you ever need an example to demonstrate the miraculous advances of modern medicine, consider using chronic hepatitis C. It inflicts about 6 per 1000 of Canadians and is the commonest reason for liver transplant in most studies. Yet until 1989, when the virus was first cloned, this condition was so poorly understood that it was labelled as what it wasn't - it was called hepatitis non-A, non-B because there was insufficient evidence to even appreciate that it was one disease, let alone an infection. Today it can be cured by taking a safe drug regimen for 6-24 wk, depending on the virus strain, previous treatments, and the degree of liver damage. This recent study showed that sofosbuvir (nucleoside polymerase inhibitor) and ledispavir (NS5A inhibitor) led to a 99% cure rate in genotype 1 (the most common) infection with only minimal side-effects. These antiviral drugs are designer drugs: specifically tailored in the laboratory to combat pathogenic features of the hepatitis C virus.



**Treatment of Hepatitis C: A Systematic Review**
JAMA 2014;312(6):631-40
**Purpose**: To evaluate the evidence for the safety, efficacy, and tolerability of interferon and non-interferon based, oral therapies in the treatment of Hepatitis C virus (HCV).
**Study**: Literature review of phase 2, 3, and 4 studies published from January 1, 2009 – May 30, 2014, with data graded according to Oxford Centre for Evidence-Based Medicine criteria.
**Population**: 19, 063 adult patients infected with HCV genotype 1, 2, or 3 with or without HIV coinfection.
**Outcome**: Sustained virologic response (SVR) of undetectable plasma HCV RNA at 12 or 24 wk post-therapy.
**Results**: Achievement of SVR was more difficult in HCV genotype 1 patients. Treatment of HCV genotype 1 patients with sofosvubir with pegylated interferon and ribavirin yielded high rates of SVR (89-90%) and shorter duration of therapy. HCV genotype 2 or 3 patients treated with sofosbuvir and ribavirin alone achieved SVR of 82-93% and 80-95% for genotype 2 at 12 wk and genotype 3 at 24 wk, respectively. Patients with HCV and HIV coinfection with compensated cirrhosis should be treated in the same manner as HCV-monoinfected patients.
**Conclusions**: High SVR rates can be achieved for HCV patients with or without HIV coinfection using shorter durations of non-interferon therapies. HCV genotype 1 patients are likely to benefit from co-treatment with interferon and non-interferon therapies.

**Table 19. Characteristics of the Viral Hepatitides**

| | HAV | HBV | HCV | HDV | HEV | CMV | EBV | Yellow Fever |
|---|---|---|---|---|---|---|---|---|
| **Virus Family** | *Picornaviridae* | *Hepadnaviridae* | *Flaviviridae* | *Deltaviridae* | *Caliciviridae* | *Herpesviridae* | *Herpesviridae* | *Flavivirus* |
| **Genome** | RNA | DNA | RNA | RNA | RNA | DNA | RNA | RNA |
| **Envelope** | No | Yes | Yes | Yes | No | Yes | Yes | Yes |
| **Transmission** | Fecal-oral | Parenteral/sexual or equivalent<br>Vertical | Parenteral/sexual (transfusion, IV drug user, sexual [<HBV])<br>40% have no known risk factors | Non-parenteral (close contact in endemic areas)<br>Parenteral (blood products, IV drug user)-sexual transmission is inefficient | Fecal-oral (endemic: Africa, Asia, central America, India, Pakistan) | Close contacts, most body fluids | Saliva-oral | Vector (mosquito) |
| **Incubation** | 4-6 wk | 6 wk-6 mo | 2-26 wk | 3-13 wk | 2-8 wk | 20-60 d | 30-50 d | 3-6 d |
| **Onset** | Usually abrupt | Usually insidious | Insidious | Usually abrupt | Usually abrupt | Variable | Variable | Usually abrupt |
| **Communicability** | 2-3 wk in late incubation to early clinical phase<br>Acute hepatitis in most adults, 10% of children | HBsAg+ state highly communicable<br>Increased during third trimester or early post-partum | Communicable prior to overt symptoms and throughout chronic illness | Infectious only in presence of HBV (HBsAg required for replication) | Unknown | Variable – dormant or persistent | Communicable highest during year after primary infection but never zero | Variable, vector-dependent |
| **Chronicity** | None, although can relapse | 5% adults, 90% infants | 80%, 20% of which develop cirrhosis | 5% | None | Common; latent | Common; latent | Infection confers lifelong immunity |
| **Serology** | Anti-HAV (IgM) | See Table 18 | HCV-RNA<br>Anti-HCV (IgG/IgM) | HBsAg<br>Anti-HDV (IgG/IgM) | Anti-HEV (IgG/IgM) | Anti- CMV (IgM/IgG) | Monospot; anti-EBV IgM/IgG, EBV DNA quantitation | Anti-YF (IgM/IgG) |
| **Vaccine** | Havrix, 2 doses q6mo, combined with Twinrix at 0, 7, and 21 d | Recombivax HBTM, age 11-15, 2 doses q6mo | No | No | No | No | No | YF-VAX, 1 dose booster q10yr |
| **Management** | General hygiene<br>Treat close contacts (anti-HAV Ig)<br>Prophylaxis for high-risk groups (HAV vaccine ± HAV Ig) unless immune | Prevention: HBV vaccine and/or hepatitis B Ig (HBIG) for needlestick, sexual contact, infants of infected mothers unless already immune<br>Rx: oral antivirals vs. interferon if indications met | Prevention: no vaccine<br>Rx: interferon + ribavirin ± protease inhibitor; although all oral anti-viral (IFN-free) therapy now available is highly efficacious | Prevention: HBV vaccine | Prevention: general hygiene, no vaccine | In high risk transplant patients: CMV IG and anti-virals (ganciclovir, valganciclovir) | Supportive treatment post infection | Prevention<br>Supportive treatment post infection |
| **Acute Mortality** | 0.1-0.3% | 0.5-2% | 1% | 2-20% coinfection with HBV, 30% superinfection<br>Predisposes HBV carriers to more severe hepatitis and faster progression to cirrhosis | 1-2% overall, 10-20% in pregnancy | Rare in immunocompetent adults | Rare | 20-60% in developing countries |
| **Oncogenicity** | No | Yes | Yes | Yes | No | No | Yes | No |
| **Complications** | Can cause acute liver failure and subsequent death (<1-5%) | Hepatocellular carcinoma secondary to cirrhosis, serum sickness-like syndrome, glomerulonephritis, cryoglobulinemia, polyarteritis nodosa, porphyria cutanea tarda | Hepatocellular carcinoma in 2-5% of cirrhosis per yr, cryoglobulinemia, B-cell non-Hodgkin lymphoma | Leukocytoclastic vasculitis, membranous glomerulonephropathy | Mild, except in third trimester (10-20% fulminant liver failure) | 5% of newborns with multiple handicaps<br>Immunocomprimised patients at risk of CMV-induced hepatitis, retinitis, colitis, esophagitis, pneumonitis | Associated with Burkitt's lymphoma and nasopharyngeal carcinoma (rare in Western world) | Can cause a recurrent toxic phase with liver damage, GI bleeding, and high mortality rates |

# Autoimmune Liver Disease

- diagnosis of exclusion: rule out viruses, drugs/alcohol, metabolic, or genetic causes
- can be severe: 40% mortality at 6 mo without treatment
- extrahepatic manifestations
  - sicca, Raynaud's, thyroiditis, Sjögren's, arthralgias
  - hypergammaglobulinemia (particularly elevated IgG)
  - typical auto-antibodies: antinuclear antibody (ANA) and/or anti-smooth muscle antibody
  - infrequently may see anti-LKM elevation (liver kidney microsome), especially in children
  - can have false positive viral serology (especially anti-HCV)
  - biopsy – periportal (zone 1) and interface inflammation and necrosis
- treatment: corticosteroids (80% respond) ± azathioprine (without this, most will relapse as corticosteroids are withdrawn)

# Drug-Induced Liver Disease

**Table 20. Classification of Hepatotoxins**

| | Direct | Indirect |
|---|---|---|
| **Example** | Acetaminophen, CCl4 | Phenytoin, INH |
| **Dose-Dependence** | Usual | Unusual |
| **Latent Period** | Hours-days | Weeks-months |
| **Host Factors** | Not important | Very important |
| **Predictable** | Yes | No (idiosyncratic) |

- many different patterns of liver injury (i.e. hepatocellular, cholestatic, mixed, granulomatous, acute liver failure) can be seen in drug-induced liver injury and thus this requires a high index of suspicion.
- see: LiverTox for Information regarding drug-specific risks and patterns of hepatotoxicity (http://livertox.nih.gov)

**Hy's Law**: drug-induced hepatocellular jaundice indicates a mortality of at least 10%

### Specific Drugs

- acetaminophen
  - metabolized by hepatic cytochrome P450 system
  - can cause acute liver failure (transaminases >1000 U/L followed by jaundice and encephalopathy)
  - requires 10-15 g in healthy, 4-6 g in alcoholics/anticonvulsant users
  - mechanism: high acetaminophen dose saturates glucuronidation and sulfation elimination pathways → reactive metabolite is formed → covalently binds to hepatocyte membrane
  - presentation
    - first 24 h: nausea and vomiting (usually within 4-12 h of overdose)
    - 24-48 h: asymptomatic, but ongoing hepatic necrosis resulting in increased transaminases
    - >48 h: continued hepatic necrosis possibly complicated with acute liver failure or resolution
    - note: potential delay in presentation in sustained-release products
  - blood levels of acetaminophen correlate with the severity of hepatic injury, particularly if time of ingestion known
  - therapy
    - gastric lavage/emesis (if <2 h after ingestion)
    - oral activated charcoal
    - N-acetylcysteine (NAC, Mucomyst®) can be given PO or IV (most effective within 8-10 h of ingestion, but should be given no matter when time of ingestion)
      - promotes hepatic glutathione regeneration
    - no recorded fatal outcomes if NAC given before increase in transaminases
- chlorpromazine: cholestasis in 1% after 4 wk; often with fever, rash, jaundice, pruritus, and eosinophilia
- INH (isoniazid)
  - 20% develop elevated transaminases but <1% develop clinically significant disease
  - susceptibility to injury increases with age
- methotrexate
  - causes fibrosis/cirrhosis; increased risk in the presence of obesity, DM, alcoholism (i.e. with underlying risk for pre-existing fatty liver)
  - scarring develops without symptoms or changes in liver enzymes, therefore biopsy may be needed in long-term treatment
- amiodarone: can cause same histology and clinical outcome as alcoholic hepatitis
- others: azoles, statins, methyldopa, phenytoin, propylthiouracil (PTU), rifampin, sulfonamides, tetracyclines
- herbs: chaparral, Chinese herbs (e.g. germander, comfrey, bush tea)

# Wilson's Disease

### Definition

- autosomal recessive defect in copper elimination (gene ATP7B)

### Etiology

- decreased biliary excretion of copper plus decreased incorporation of copper into ceruloplasmin
- worldwide incidence 1/40,000

### Clinical Features

- liver: acute hepatitis, acute liver failure, chronic active hepatitis, cirrhosis, low risk of hepatocellular carcinoma
- eyes: Kayser-Fleischer rings (copper deposits in Descemet's membrane); more common in patients with CNS involvement, present in only 50% of isolated liver involvement
- CNS: basal ganglia (wing flapping tremor, Parkinsonism), cerebellum (dysarthria, dysphagia, incoordination, ataxia), cerebrum (psychosis, affective disorder)
- kidneys: Fanconi's syndrome (proximal tubule transport defects) and stones
- blood: intravascular hemolysis; may be initial presentation in fulminant hepatitis
- joints: arthritis, bone demineralization, calcifications

**Clinical Manifestations of Wilson's Disease**

**ABCD**
**A**sterixis
**B**asal ganglia degeneration: suspect if parkinsonian features in the young
**C**eruloplasmin decreases
**C**irrhosis
**C**orneal deposits (Kayser-Fleischer ring)
**C**opper
**D**ementia

### Investigations
- suspect if increased liver enzymes with clinical manifestations at young age (<40); especially combination of liver disease with dystonia, psychiatric symptoms
- screening tests
  1. reduced serum ceruloplasmin (<50% of normal)
  2. Kayser-Fleischer rings (usually require slit-lamp examination)
  3. increased urinary copper excretion (measure 24-hour urine copper)
- gold standard
  1. increased copper on liver biopsy by quantitative assay
  2. genetic analysis imperfect as many mutations in ATP7B are possible

### Treatment
- 4 drugs available
  1. penicillamine chelates copper, poorly tolerated
  2. trientine chelates copper
  3. zinc impairs copper excretion in stool and decreases copper absorption from gut
  4. tetrathiomolybdate preferred if neurological involvement
- hepatic presentations are best treated with a trientine + zinc combination; neurologic presentations are best treated with zinc; maintenance therapy with zinc
- liver transplant in severe cases of liver failure
- screen relatives

## Hemochromatosis

### Definition
- excessive iron storage causing multiorgan system dysfunction (liver, in particular) with total body stores of iron increased to 20-40 g (normal 1 g)

### Etiology
- primary (hereditary) hemochromatosis
  - hepcidin deficiency results in ongoing gut absorption of iron despite adequate iron stores
- secondary hemochromatosis
  - parenteral iron overload (e.g. transfusions)
  - chronic hemolytic anemia: thalassemia, pyruvate kinase deficiency
  - excessive iron intake

### Epidemiology
- hereditary hemochromatosis most common in Northern European descent
- primarily due to the recessive gene, *HFE* (or high iron), which has a homozygous genetic prevalence of 1/400

### Clinical Features
- usually presents with trivial elevation in serum transaminases
- liver: cirrhosis (less common nowadays due to earlier detection), HCC (200x increased risk)
- pancreas: DM, chronic pancreatitis
- skin: bronze or grey (due to melanin, not iron)
- heart: dilated cardiomyopathy
- pituitary: hypogonadotropic hypogonadism (impotence, decreased libido, amenorrhea)
- joints: arthralgia (any joint, but especially MCP joints), chondrocalcinosis

**Hemochromatosis Clinical Features ABCD**
- Arthralgia
- Bronze skin
- Cardiomyopathy, cirrhosis of liver
- Diabetes (pancreatic damage)
- Hypogonadism (anterior pituitary damage)

### Investigations
- screening for individuals with clinical features and/or family history (1/4 chance of sibling having the disease)
  - transferrin saturation (free $Fe^{2+}$/TIBC) >45%
  - serum ferritin >400 ng/mL
  - HFE gene analysis: 90% of primary hemochromatosis involves C282Y allele, while H63D and S65C alleles also commonly involved and screened
- liver biopsy (generally used to detect cirrhosis or if potential for other causes of liver disease)
  - markers of advanced fibrosis: if any of the following are present at the time of diagnosis → age >40, elevated liver enzymes, or ferritin >1000
  - considered if compound heterozygote and potential other cause of liver injury (e.g. fatty liver, etc.)
  - if C282Y/C282Y and no markers of advanced fibrosis, then biopsy generally not needed
- HCC screening if cirrhosis

Ferritin may never normalize if other causes of high ferritin present (e.g. fatty liver from metabolic syndrome or alcohol)

Gene mutation not 100% penetrant, so not all with homozygous gene defect have clinically significant iron overload

### Treatment
- phlebotomy: weekly or q2wk then lifelong maintenance phlebotomies q2-6mo
- deferoxamine if phlebotomy contraindicated (e.g. cardiomyopathy, anemia)
- primary hemochromatosis responds well to phlebotomy
- secondary hemochromatosis usually requires chelation therapy (administration of agents that bind and sequester iron, and then excreted)

### Prognosis
- normal life expectancy if treated before the development of cirrhosis or DM

# Alcoholic Liver Disease

## Definition
- spectrum of diseases, ranging from:
  - fatty liver (common amongst individuals with alcohol use disorder): reversible if alcohol stopped
  - alcoholic hepatitis (35% of individuals with alcohol use disorder): usually reversible if alcohol stopped
  - cirrhosis (10-15% of individuals with alcohol use disorder): potentially irreversible

## Pathophysiology
- several mechanisms, poorly understood
- ethanol oxidation to acetaldehyde
  - reduces NAD+ to NADH; increased NADH decreases ATP supply to liver, impairing lipolysis so fatty acids and triglycerides accumulate in liver
  - binds to hepatocytes evoking an immune reaction
- EtOH increases gut permeability leading to increased bacterial translocation
- alcohol metabolism causes:
  - relative hypoxia in liver zone III (near central veins; poorly oxygenated) > zone I (around portal tracts, where oxygenated blood enters)
  - necrosis and hepatic vein sclerosis
- histology of alcoholic hepatitis
  - ballooned (swollen) hepatocytes often containing Mallory bodies, characteristically surrounded by neutrophils
  - large fat globules
  - fibrosis: space of Disse and perivenular

## Clinical Features
- >2-3 standard drinks/d in females and >3-6 standard drinks/d in men for >10 yr leads to cirrhosis, but only in about 10-20% of those who consume this amount daily on a continuous basis; cirrhosis risk increases with amount of alcohol consumed above threshold
- clinical findings do not accurately predict type of liver involvement
- fatty liver
  - mildly tender hepatomegaly; jaundice rare
  - mildly increased transaminases <5x normal
- alcoholic hepatitis
  - variable severity: mild to fatal liver failure
  - mild: stops drinking because feels unwell, resumes when feeling better (if assessed, findings of hepatitis, potentially mild jaundice, and mildly elevated INR)
  - severe: stops drinking but feels unwell, low grade fever, RUQ discomfort, increased white blood cell count – mimics RLL pneumonia and cholecystitis

## Investigations
- blood tests are non-specific, but in general
  - AST:ALT >2:1 (both usually <300)
  - CBC: increased MCV, increased WBC often seen with alcoholic hepatitis but not necessarily in other alcohol-related liver injury
  - increased GGT

## Treatment
- alcohol cessation (see Psychiatry, PS27)
  - Alcoholics Anonymous, disulfiram, naltrexone, acamprosate
- multivitamin supplements (especially thiamine)
- caution with drugs metabolized by the liver
- prednisolone if severe alcoholic hepatitis based on Maddrey's discriminant function or MELD score as described in Prognosis
  - pentoxifylline less used since most definitive trial did not demonstrate efficacy

## Prognosis
- Maddrey's discriminant function (based on PT and bilirubin) and Model for End-Stage Liver Disease (MELD) predict mortality and guide treatment (consideration for corticosteroids for severe disease based on Maddrey ≥ 32 or MELD ≥21)
- fatty liver: complete resolution with cessation of alcohol intake
- alcoholic hepatitis mortality
  - immediate: 30%-60% in the first 6 mo if severe
  - with continued alcohol: 70% in 5 yr
  - with cessation: 30% in 5 yr





**Standard Drink Equivalent**
1 standard drink= 14 g EtOH
= 12 oz beer (5% alcohol)
= 5 oz wine (12-17%)
= 3 oz fortified wine (17-22%)
= 1.5 oz liquor (40%)
Tip: percentage alcohol multiplied by oz in 1 standard drink roughly equals 60



**Biopsy + Histology of Alcoholic Hepatitis (triad)**
- Hepatocyte necrosis with surrounding inflammation in zone III
- Mallory bodies (intracellular eosinophilic aggregates of cytokeratins)
- Chicken-wire fibrosis (network of intralobular connective tissue surrounding cells and venules)



**GI Complications of Alcohol Abuse**
- Esophagus
  - Mallory-Weiss tear
  - Esophageal varices (secondary to portal hypertension)
- Stomach
  - Alcoholic gastritis
- Pancreas
  - Acute pancreatitis
  - Chronic pancreatitis
- Liver
  - Alcoholic hepatitis
  - Fatty liver
  - Cirrhosis
  - Hepatic encephalopathy
  - Portal hypertension
  - Ascites
  - HCC

# Non-Alcoholic Fatty Liver Disease

### Definition
- spectrum of disorders characterized by macrovesicular hepatic steatosis, sometimes with inflammation and/or fibrosis
- most common cause of liver disease in North America

### Etiology
- pathogenesis not well elucidated; insulin resistance implicated as key mechanism, leading to hepatic steatosis
- histological changes indistinguishable from those of alcoholic hepatitis despite negligible history of alcohol consumption

### Risk Factors
- likely a component of the metabolic syndrome along with obesity, T2DM, HTN, hypertriglyceridemia
- rapid weight loss or weight gain

### Clinical Features
- often asymptomatic
- may present with fatigue, malaise, and vague RUQ discomfort
- elevated serum triglyceride/cholesterol levels and insulin resistance

### Investigations
- elevated serum AST, ALT ± ALP; AST/ALT <1
- presents as echogenic liver texture on ultrasound
- non-invasive testing of fibrosis: FIB4, NAFLD fibrosis score, Fibrotest, FibroScan®
- liver biopsy cannot distinguish fatty liver from alcohol vs non-alcoholic fatty liver, but considered when investigating alternative etiologies or assessing for level of fibrosis

### Treatment
- mainstay is gradual weight loss (0.5-1 kg/wk) as rapid weight loss can worsen liver disease
  - ideally, aim to lose at least 7-10% of body weight
- some evidence for vitamin E (800 U daily) if there is hepatic inflammation
- some evidence for benefits of coffee drinking (3 cups/d) and vitamin D

### Prognosis
- most die from cardiovascular or cerebrovascular disease
- better prognosis than alcoholic hepatitis
  - <25% progress to cirrhosis over a 7-10 yr period
- risk of progression increases if inflammation or scarring occurs alongside fat infiltration (non-alcoholic steatohepatitis)
- other clinical indicators of unfavourable prognosis: DM, age, metabolic syndrome, higher levels of fibrosis

# Acute Liver Failure (formerly Fulminant Hepatic Failure)

### Definition
- severe decline in liver function characterized by coagulation abnormality (INR >1.5) and encephalopathy
- in setting of previously normal liver
- rapid (<26 wk duration)

### Etiology
- drugs (especially acetaminophen), hepatitis B (measure anti-HBc, IgM fraction because sometimes HBV-DNA and even HBsAg rapidly becomes negative), hepatitis A, hepatitis C (rare), ischemic, idiopathic

### Treatment
- correct hypoglycemia, monitor level of consciousness, prevent GI bleeding with PPI, monitor for infection and multiorgan failure (usually requires ICU)
- consider liver biopsy before INR becomes too high
- chief value of biopsy is to exclude chronic disease, less helpful for prognosis
- liver transplant (King's College criteria can be used as prognostic indicator): consider early, especially if time from jaundice to encephalopathy >7 d (e.g. not extremely rapid), age <10 or >40, cause is drug or unknown, bilirubin >300 μmol/L, INR >3.5, creatinine >200 μmol/L

# Cirrhosis

## Definition

- liver damage characterized by diffuse distortion of the basic architecture with fibrosis and formation of regenerative nodules
- Biopsy gold standard for diagnosis
- Stage 1 cirrhosis is compensated and asymptomatic, can last for 10-20 yr with almost normal life expectancy
- Stage 2 cirrhosis is decompensation, typically development of ascites (most common), variceal bleeding, encephalopathy, characteristically presents abruptly even though histologically the liver fibrosis is gradually progressive

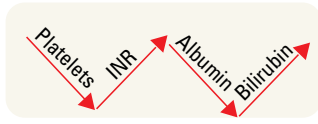



**Figure 13. Progression of liver dysfunction based on liver function tests – the "W"**

## Etiology

- fatty liver (alcoholic or non-alcoholic fatty liver disease)
- chronic viral hepatitis (B, B+D, C; not A or E)
- autoimmune hepatitis
- drugs (e.g. chronic methotrexate or amiodarone use)
- hemochromatosis
- primary biliary cholangitis
- chronic hepatic congestion
  - cardiac cirrhosis (chronic right heart failure, constrictive pericarditis)
  - hepatic vein thrombosis (Budd-Chiari)
- cryptogenic (i.e. no identifiable cause, although many of these patients may represent "burnt-out non-alcoholic steatohepatitis [NASH]")
- rare: Wilson's disease, Gaucher's disease, α1-antitrypsin deficiency

## Investigations

- definitive diagnosis is histologic (liver biopsy)
- other tests may be suggestive
  - blood work: fall in platelet count <150 is the earliest finding, followed many years later with rise in INR, fall in albumin, rise in bilirubin, fall in glucose level (pre-terminal event)
  - FibroTest: combination of various clinical and biochemical markers that can predict degree of fibrosis
  - imaging
    - U/S is the primary imaging modality but only finds advanced cirrhosis
    - CT to look for varices, nodular liver texture, splenomegaly, ascites
    - Transient Ultrasound Elastograhy (FibroScan®): non-invasive tool using elastography (variable availability) for measuring liver compliance
      - rapidly replacing liver biopsy to determine extent of liver fibrosis and make the diagnosis of cirrhosis
- gastroscopy: varices or portal hypertensive gastropathy

## Treatment

- treat underlying disorder
- decrease insults (e.g. alcohol cessation, hepatotoxic drugs, immunize for Hep A and B if non-immune)
- follow patient for complications (esophageal varices, ascites, HCC defines stage 2 cirrhosis)
- prognosis: Child-Pugh Score and MELD score
- liver transplantation for end-stage disease if no alcohol for >6 mo; use MELD score

**MELD-Na (Model for End-Stage Liver Disease)**

- Predicts 3 mo survival and used to stratify patients on transplant list
- Based on creatinine, INR, total bilirubin, and serum sodium concentration

**Cirrhosis Complications**

**VARICES**
**V**arices
**A**scites/**A**nemia
**R**enal failure (hepatorenal syndrome)
**I**nfection
**C**oagulopathy
**E**ncephalopathy
**S**epsis

**Table 21. Child-Pugh Score and Interpretation**

| Classification | 1 | 2 | 3 |
|---|---|---|---|
| Serum bilirubin (μmol/L) | <34 | 34-51 | >51 |
| Serum albumin (g/L) | >35 | 28-35 | <28 |
| INR | <1.7 | 1.7-2.3 | >2.3 |
| Presence of ascites | Absent | Controllable | Refractory |
| Encephalopathy | Absent | Minimal | Severe |
| **Interpretation** | | | |
| **Points** | **Class** | **Life Expectancy** | **Perioperative Mortality** |
| 5-6 | A | 15-50 yr | 10% |
| 7-9 | B | Candidate for transplant | 30% |
| 10-15 | C | 1-3 mo | 82% |

Score: 5-6 (Child's A), 7-9 (Child's B), 10-15 (Child's C)
*Note: Child's classification is rarely used for shunting (TIPS or other surgical shunts), but is still useful to quantitate the severity of cirrhosis

### Complications

- hematologic changes in cirrhosis
  - pancytopenia from hypersplenism: platelets first, then WBC, then hemoglobin
  - decreased clotting factors resulting in elevated INR
  - relationship of INR to bleeding tendency is controversial; some patients may be hypocoagulable, others may be hypercoagulable
- variceal bleeds
  - half of patients with cirrhosis have gastroesophageal varices and one-third of these develop hemorrhage with an overall mortality of >30%
  - hepatic venous pressure gradient (HVPG) ≥10 mmHg is the strongest predictor of variceal development
  - treatment: resuscitation, antibiotic prophylaxis, vasoactive drugs (e.g. octreotide IV) combined with endoscopic band ligation or sclerotherapy, Transjugular Intrahepatic Portosystemic Shunt (TIPS)
- renal failure in cirrhosis
  - classifications
    - pre-renal (usually due to over-diuresis)
    - acute tubular necrosis
    - Hepatorenal Syndrome (HRS)
      - Type I: sudden and acute renal failure (rapid doubling of creatinine over 2 wk)
      - Type II: gradual increase in creatinine with worsening liver function (creatinine doubling over years)
    - HRS can occur at any time in severe liver disease, especially after:
      - overdiuresis or dehydration, such as diarrhea, vomiting, etc.
      - GI bleed
      - sepsis
    - treatment for hepatorenal syndrome (generally unsuccessful at improving long-term survival)
      - for type I HRS: octreotide + midodrine + albumin (increases renal blood flow by increasing systemic vascular resistance)
      - definitive treatment is liver transplant
- hepatopulmonary syndrome
  - majority of cases due to cirrhosis, though can be due to other chronic liver diseases, such as non-cirrhotic portal HTN
  - thought to arise from ventilation-perfusion mismatch, intrapulmonary shunting and limitation of oxygen diffusion, failure of damaged liver to clear circulating pulmonary vasodilators vs. production of a vasodilating substance by the liver
  - clinical features
    - hyperdynamic circulation with cardiac output >7 L/min at rest and decreased pulmonary + systemic resistance (intrapulmonary shunting)
    - dyspnea, platypnea (increase in dyspnea in upright position, improved by recumbency), and orthodeoxia (desaturation in the upright position, improved by recumbency)
    - diagnosis via contrast-enhanced echocardiography: inject air bubbles into peripheral vein; air bubbles appear in left ventricle after third heartbeat (normal = no air bubbles; in ventricular septal defect, air bubbles seen <3 heart beats)
    - only proven treatment is liver transplantation

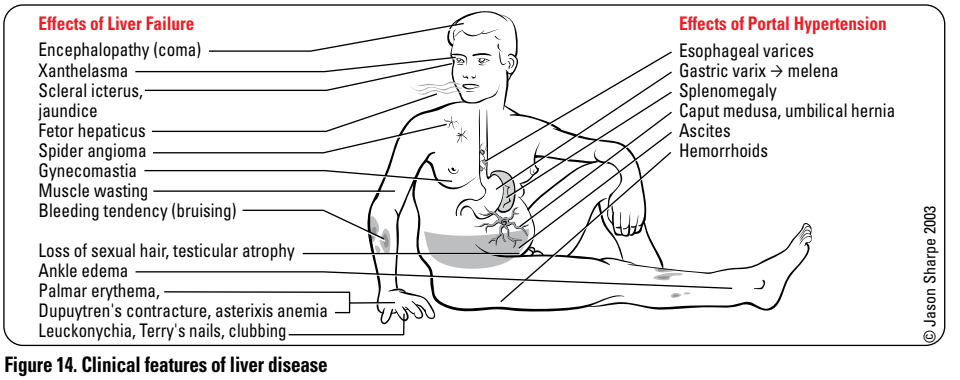



**Figure 14. Clinical features of liver disease**

Usual causes of death in cirrhosis: renal failure (hepatorenal syndrome), sepsis, GI bleed, or HCC

**Hepatorenal Syndrome vs. Pre-Renal Failure – Difficult to Differentiate**
- Similar blood and urine findings
- Urine sodium: very low in hepatorenal; low in pre-renal
- Intravenous fluid challenge: giving volume expanders improves pre-renal failure, but not hepatorenal syndrome

**Hepatopulmonary Syndrome Clinical Triad**
- Liver disease
- Increased alveolar-arterial gradient while breathing room air
- Evidence for intrapulmonary vascular abnormalities

Fibrosis may regress and disappear if cause of liver injury is treated or resolves

## Hepatocellular Carcinoma

- see General Surgery, GS49

## Liver Transplantation

- see General Surgery, GS50

# Portal Hypertension

### Definition
- pressure gradient between hepatic vein pressure and wedged hepatic vein pressure (corrected sinusoidal pressure) >5 mmHg

### Pathophysiology
- 3 sites of increased resistance (remember pressure = flow x resistance)
  - pre-sinusoidal (e.g. portal vein thrombosis, schistosomiasis, sarcoidosis)
  - sinusoidal (e.g. cirrhosis, alcoholic hepatitis)
  - post-sinusoidal (e.g. right-sided heart failure, hepatic vein thrombosis, veno-occlusive disease, constrictive pericarditis)

### Complications
- GI bleeding from varices in esophagus, less commonly in stomach, even less frequently from portal hypertensive gastropathy
- ascites
- hepatic encephalopathy
- thrombocytopenia
- renal dysfunction
- sepsis
- arterial hypoxemia

### Treatment
- non-selective β-blockers (propanolol, nadolol, carvedilol) decrease risk of bleeding from varices
- TIPS: to decrease portal venous pressure
  - radiologically inserted stent between portal and hepatic vein via transjugular vein catheterization and percutaneous puncture of portal vein
  - can be used to stop acute bleeding or prevent rebleeding or treat ascites
  - complications: hepatic encephalopathy, deterioration of hepatic function
  - contraindicated with severe liver dysfunction, uncontrolled hepatic encephalopathy, and congestive heart failure
  - most commonly used as a "bridge" to liver transplant
- other surgically created shunts: portacaval, distal spleno-renal (Warren shunt) - all used only rarely in the modern era

**Portal Hypertension**

**Signs**
- Esophageal varices
- Melena
- Splenomegaly
- Ascites
- Hemorrhoids

**Management**
- β-blockers
- Nitrates
- Shunts (e.g. TIPS)

# Hepatic Encephalopathy

### Definition
- spectrum of potentially reversible neuropsychiatric syndromes secondary to liver disease diagnosed after ruling out other causes for symptoms (e.g. structural/metabolic)

### Pathophysiology
- portosystemic shunt around hepatocytes and decreased hepatocellular function increase level of systemic toxins (believed to be ammonia from gut, mercaptans, fatty acids, amino acids) which go to the brain

### Precipitating Factors
- nitrogen load (GI bleed, protein load from food intake, renal failure, constipation)
- drugs (narcotics, CNS depressants)
- electrolyte disturbance (hypokalemia, alkalosis, hypoxia, hypovolemia)
- infection (spontaneous bacterial peritonitis)
- deterioration in hepatic function or superimposed liver disease

### Stages
- I: apathy, restlessness, reversal of sleep-wake cycle, slowed intellect, impaired computational abilities, impaired handwriting
- II: asterixis, lethargy, drowsiness, disorientation
- III: stupor (rousable), hyperactive reflexes, extensor plantar response (upgoing Babinski)
- IV: coma (response to painful stimuli only)

### Investigations
- clinical diagnosis: supported by laboratory findings and exclusion of other neuropsychiatric diseases
- rule out
  - non-liver-related neuropsychiatric disease in a patient with liver problems (e.g. alcohol withdrawal or intoxication, sedatives, subdural hematoma, metabolic encephalopathy)
  - causes of metabolic encephalopathy (e.g. renal failure, respiratory failure, severe hyponatremia, hypoglycemia)
- characteristic EEG findings: diffuse (non-focal), slow, high amplitude waves
- serum ammonia levels increased, but not often necessary to measure in routine clinical use

**Precipitating Factors for Hepatic Encephalopathy**

**Hepatics**
**H**emorrhage in GI tract/**H**ypokalemia
**E**xcess dietary protein
**P**aracentesis
**A**lkalosis/**A**nemia
**T**rauma
**I**nfection
**C**olon surgery
**S**edatives

**A Randomized, Double-Blind, Controlled Trial Comparing Rifaximin Plus Lactulose With Lactulose Alone in Treatment of Overt Hepatic Encephalopathy**
American J Gastroenterol 2013;108:1458-63
**Study**: prospective double-blind RCT.
**Objectives**: Efficacy and safety of rifaximin plus lactulose vs. lactulose alone for treatment of overt HE.
**Results**: Of the patients, 48 (76%) in group A (lactulose plus rifaximin 1200 mg/d, n=63) compared with 29 (50.8%) in group B (lactulose (n=57) plus placebo) had complete reversal of HE (P<0.004). There was a significant decrease in mortality after treatment with lactulose plus rifaximin vs. lactulose and placebo (23.8% vs. 49.1%, P<0.05). There were significantly more deaths in group B because of sepsis (group A vs. group B: 7:17, P=0.01), whereas there were no differences because of gastrointestinal bleed (group A vs. group B: 4:4, P=nonsignificant (NS)) and hepatorenal syndrome (group A vs. group B: 4:7, P=NS). Patients in the lactulose plus rifaximin group had shorter hospital stay (5.8±3.4 vs. 8.2±4.6 d, P=0.001).
**Conclusion**: Combination of lactulose plus rifaximin is more effective than lactulose alone in the treatment of overt HE.

### Treatment
- treat underlying precipitating factors
- decrease generation of nitrogenous compounds
  - routine protein restriction is no longer recommended given patients generally have concurrent malnutrition and muscle wasting; however, vegetable protein is better tolerated than animal protein
  - lactulose: titrated to achieve 2-3 soft stools/d
    - prevents diffusion of NH3 (ammonia) from the colon into blood by lowering pH and forming non-diffusible NH4 (ammonium)
    - serves as a substrate for incorporation of ammonia by bacteria, promotes growth in bowel lumen of bacteria which produce minimal ammonia
    - also acts as a laxative to eliminate nitrogen-producing bacteria from colon
- oral rifaximin for both acute treatment and maintenance therapy has high level evidence for efficacy
- best acute treatment in comatose patient is lactulose enemas

## Ascites

### Definition
- accumulation of excess fluid in the peritoneal cavity

### Etiology

**Table 22. Serum-Ascites Albumin Gradient in the Evaluation of Ascites**

| Serum [Alb] – Ascitic [Alb] >11 g/L (1.1 g/dL)<br>Portal Hypertension Related | Serum [Alb] – Ascitic [Alb] <11 g/L (1.1 g/dL)<br>Non-Portal Hypertension Related |
|---|---|
| Cirrhosis/severe hepatitis | Peritoneal carcinomatosis |
| Chronic hepatic congestion (right heart failure, Budd-Chiari) | TB |
| Massive liver metastases | Pancreatic disease |
| Myxedema | Serositis |
| | Nephrotic syndrome* |

* In nephrotic syndrome: decreased serum [Alb] to begin with therefore gradient not helpful

### Pathophysiology
- key factor in pathogenesis is increased sodium (and water) retention by the kidney for reasons not fully understood. Theories include:
  - underfill hypothesis
  - overfill hypothesis
  - peripheral arterial vasodilation theory (most popular): as portal hypertension develops in cirrhosis, production of local mediators such as nitric oxide leads to splanchnic arterial vasodilation, ultimately pulling blood away from the systemic circulation and resulting in reduced effective arterial volume, which causes compensatory sodium and fluid retention by the kidneys (i.e. circulatory volume is increased, as per the overfill hypothesis, but effective volume is decreased as per the underfill hypothesis)

**Underfill Hypothesis**
First step in ascites formation is increased portal pressure and low oncotic pressure (e.g. low serum albumin) driving water out of the splanchnic portal circulation into abdominal cavity; the resulting decreased circulating volume causes secondary sodium retention by the kidney

**Overfill Hypothesis**
Cirrhosis directly causes increased sodium retention by the kidney in the absence of hypovolemia and ascites arises secondarily

### Diagnosis
- abdominal ultrasound
- physical exam (clinically detectable when >500 mL)
  - bulging flanks, shifting dullness, fluid-wave test positive
  - most sensitive symptom: ankle swelling

### Investigations
- diagnostic paracentesis
  - 1st aliquot: cell count and differential
  - 2nd aliquot: chemistry (especially albumin, but also total protein; amylase if pancreatitis; TG and chylomicrons if turbid and suspect chylous ascites)
  - 3rd aliquot: C&S, Gram stain
  - 4th aliquot: cytology (usually positive in peritoneal carcinomatosis)

### Treatment
- diuretic-sensitive ascites
  - $Na^+$ restriction (daily sodium intake <2 g)
  - diuretics: spironolactone, furosemide
  - aim for weight loss 0.5-1 kg/d, more if concomitant peripheral edema (which is mobilized quicker than ascitic fluid); overly rapid weight loss increases risk of renal failure
  - if target weight loss is not achieved and there are no complications, increase dose to achieve target while monitoring for complications
- refractory ascites (diuretics are inadequate or not tolerated)
  - therapeutic paracentesis with intravenous albumin
  - TIPS in an appropriate patient (no contraindications) with potential transplant-free survival advantage
  - liver transplantation should be considered in every case, since development of ascites in patients with cirrhosis is associated with 50% 2 yr mortality

### Complication: Primary/Spontaneous Bacterial Peritonitis

- primary/spontaneous bacterial peritonitis (SBP)
  - complicates ascites, but does not cause it (occurs in 10% of cirrhotic ascites); higher risk in patients with GI bleed
  - 1/3 of patients are asymptomatic, thus do not hesitate to do a diagnostic paracentesis in ascites even if no clinical indication of infection
  - fever, chills, abdominal pain, ileus, hypotension, worsening encephalopathy, acute kidney injury
  - Gram-negatives compose 70% of pathogens: *E. coli* (most common), *Streptococcus, Klebsiella*
- diagnosis
  - absolute neutrophil count in peritoneal fluid >0.25x109 cells/L (250 cells/mm$^3$)
  - Gram stain positive in only 10-50% of patients
  - culture positive in <80% of patients (not needed for diagnosis)
- prophylaxis: consider in patients with:
  - cirrhosis or GI bleed: ceftriaxone IV daily or norfloxacin bid x 7 d
  - previous episode of SBP: long-term prophylaxis with daily norfloxacin or TMP-SMX
- treatment
  - IV antibiotics (cefotaxime 2 g IV q8h or ceftriaxone 2 g IV daily is the treatment of choice for 5 d; modify if response inadequate or culture shows resistant organisms)
  - IV albumin (1.5 g/kg at time of diagnosis and 1 g/kg on day 3) decreases mortality by lowering risk of acute renal failure

**Serum Ascites Albumin Gradient (SAAG) = serum albumin – ascites albumin**

- >11 g/L portal HTN
  - ascitic fluid total protein >25 g/L, suggests cardiac portal hypertension
  - ascitic fluid total protein <25 g/L, suggests cirrhosis portal hypertension
- <11 g/L unrelated to portal HTN

# Biliary Tract

## Jaundice

- see Table 2 and Figures 15 and 16

### Signs and Symptoms

- dark urine, pale stools: suggests that bilirubin elevation is from direct fraction
- pruritus: suggests chronic disease, cholestasis
- abdominal pain: suggests biliary tract obstruction from stone or pancreatic tumour (obstructive jaundice)
- painless jaundice in the elderly: think of pancreatic cancer, although most patients with pancreatic cancer have pain
- kernicterus: rarely seen in adults due to maturation of blood brain barrier

### Investigations

- blood work: CBC, bilirubin (direct and total), liver enzymes (AST, ALT, ALP, GGT), liver function tests (INR/PT, PTT, albumin), amylase
- U/S or CT for evidence of bile duct obstruction (e.g. bile duct dilation)
- direct bile duct visualization
- magnetic resonance cholangiopancreatography (MRCP): non-invasive
- endoscopic ultrasound (EUS): sensitive for stones and pancreatic tumours
- endoscopic retrograde cholangiopancreatography (ERCP): invasive, most accurate, allows for therapeutic intervention
- percutaneous transhepatic cholangiography (PTC): if ERCP fails (endoscopic access not possible)

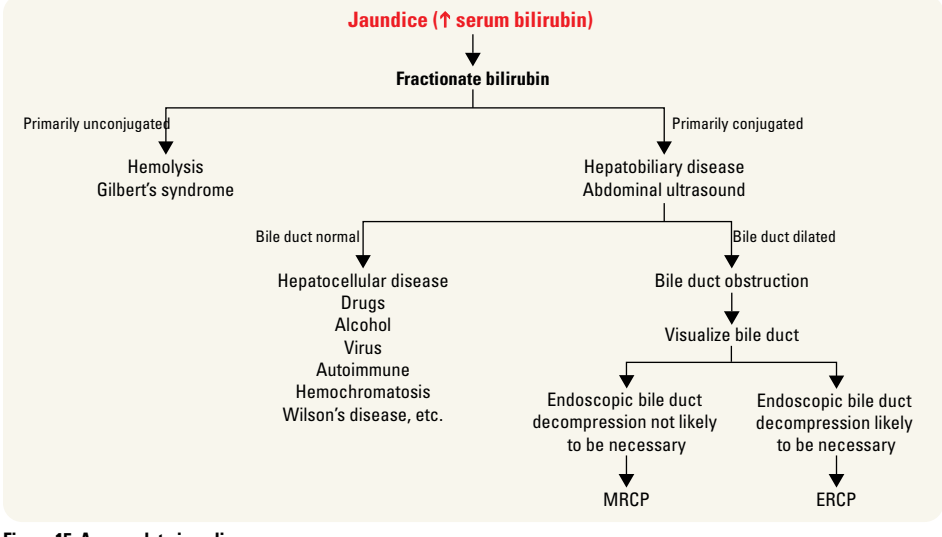



**Figure 15. Approach to jaundice**

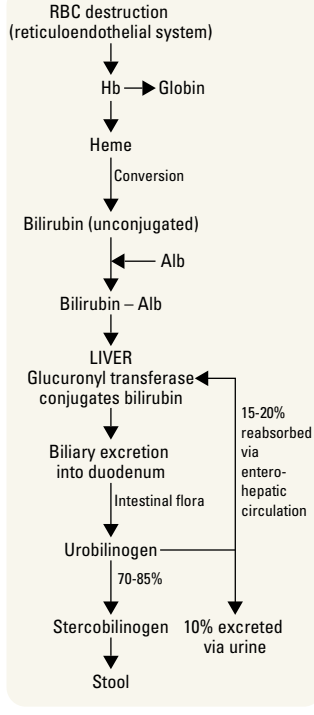



**Figure 16. Production and excretion of bilirubin**

# Gilbert's Syndrome

### Etiology/Epidemiology
- some patients have decreased hepatobiliary uptake
- affects 7% of population, especially males
- autosomal dominant, 70% due to a mutation in the UGT gene

### Clinical Features
- presents in teens-20s, often an incidental finding
- only manifestation is intermittent jaundice with increased serum unconjugated bilirubin developing most characteristically while fasting, or at times of acute illness; no other clinical implications

### Treatment
- none indicated (entirely benign)

**Gilbert's Syndrome vs. Crigler-Najjar Syndrome**
**Gilbert's Syndrome**: mild decrease in glucuronyltransferase activity
**Crigler-Najjar Syndrome**: complete deficiency of glucuronyltransferase

# Primary Sclerosing Cholangitis

### Definition
- narrowing of biliary tree (intra and/or extrahepatic bile ducts) from scarring

### Etiology
- primary/idiopathic (most common)
  - associated with IBD, more commonly UC, in up to 70-80% of patients (usually male) with PSC
- secondary (less common)
  - long-term choledocholithiasis
  - cholangiocarcinoma
  - surgical/traumatic injury (iatrogenic)
  - contiguous inflammatory process
  - post-ERCP
  - associated with HIV/AIDS ("HIV cholangiopathy")
  - IgG4-related disease

### Signs and Symptoms
- often insidious, may present with fatigue and pruritus
- may present with signs of episodic bacterial cholangitis secondary to biliary obstruction

### Investigations
- increased ALP (hallmark), less often increased bilirubin
- mildly increased AST, usually <300 U/L
- p-ANCA (30-80%), elevated IgM (40-50%)
- MRCP and ERCP shows narrowing and dilatations of bile ducts that may result in "beading", both intrahepatic and extrahepatic bile ducts
  - if intrahepatic narrowing only, do anti-mitochondrial antibody to rule out PBC

### Complications
- repeated bouts of cholangitis may lead to complete biliary obstruction with resultant secondary biliary cirrhosis and hepatic failure
- increased incidence of cholangiocarcinoma (10-15%): difficult to diagnose and treat

### Treatment
- image bile duct (MRCP) at least annually for early detection of cholangiocarcinoma (controversial)
- endoscopic sphincterotomy, biliary stent in selected cases of dominant common bile duct stricture
- antibiotics for cholangitis
- suppurative cholangitis requires emergency drainage of pus in common bile duct
- liver transplantation appears to be the best treatment for advanced sclerosing cholangitis (nearly 90% 1 yr survival; mean follow-up time from diagnosis to need for transplant is 10 yr)
- ursodiol: previously recommended, but studies suggest that at least in high doses it increases mortality

### Prognosis
- unfavourable regardless of treatment
- mean survival after diagnosis remains 4-10 yr

# Primary Biliary Cholangitis (formerly cirrhosis)

## Definition
- chronic inflammation and fibrous obliteration of intrahepatic bile ductules

## Etiology/Epidemiology
- likely autoimmune (associated with Sjögren's syndrome, scleroderma, CREST syndrome, rheumatoid arthritis (RA), thyroiditis)
- affects mainly middle-aged women (M:F = 1:9)

## Signs and Symptoms
- often asymptomatic
- initial symptoms: pruritus, fatigue
- chronic: jaundice and melanosis (darkening skin) and other signs of cholestasis
- end-stage: hepatocellular failure, portal HTN, ascites
- high incidence of osteoporosis

## Investigations
- increased ALP, GGT; bilirubin rises in later stage
- positive anti-mitochondrial antibodies (AMA; 95% specificity and sensitivity)
- elevated IgM
- increased serum cholesterol (mild increase in LDL, larger increase in HDL)
  - may have: xanthelasmas, xanthomas
- liver biopsy confirms diagnosis and stages severity
- normal bile duct on MRCP rules out bile duct obstruction which can mimic PBC
- recently described "overlap" syndromes with autoimmune cholangitis, autoimmune hepatitis, sclerosing cholangitis

## Treatment
- drugs that treat the underlying disease:
  - ursodiol (usual first line treatment)
  - obeticholic acid (particularly if inadequate response to urosiol)
- cholestyramine (for pruritus and hypercholesterolemia)
- calcium and vitamin D for low bone density; bisphosphonates if osteoporosis severe
- monitor for thyroid disease
- liver transplant if disease severe, progressive

## Prognosis
- can be fatal, although not all asymptomatic patients show progression

**Table 23. Primary Sclerosing Cholangitis vs. Primary Biliary Cholangitis**

| | Primary Sclerosing Cholangitis | Primary Biliary Cholangitis |
|---|---|---|
| **Predominant Gender** | Male | Female |
| **Associated Comorbidities** | IBD, especially UC | Other autoimmune disorders (Sjögren's, CREST, RA) |
| **Affected Ducts** | Both intra- and extra-hepatic | Intrahepatic only |
| **Investigations** | ERCP/MRCP (narrowing and dilatations of ducts visualized) | Anti-mitochondrial antibodies, IgM, increased lipids, liver biopsy (absence of duct narrowing on ERCP) |



**MRCP/ERCP**
- Absence of narrowing in PBC
- Narrowing of intra and extrahepatic ducts in PSC



**Endoscopic or Surgical Step-Up Approach for Infected Necrotising Pancreatitis: A Multicentre Randomised Trial**
Lancet 2018;391:51-58
**Purpose**: To compare the outcomes of endoscopic versus the standard surgical removal of infected necrotising pancreatitis.
**Study**: Randomized controlled trial.
**Population**: 98 patients with pancreatic or extrapancreatic necrosis were randomized to either endoscopic removal or surgical removal of the infected necrosis.
**Outcomes**: Major complications and death at 6 mo follow-up.
**Results**: The primary end-points of mortality and major complications was the same in the two groups, but the endoscopic group had shortened hospital stays and less pancreatic fistulas.
**Conclusions**: Three points are worth emphasizing: (1) necrotising pancreatitis is a severe disease: about 15% in each group died; (2) it is best to wait at least 4 wk after the necrosis has developed to allow it to be encapsulated; (3) the management of severe acute pancreatitis should include experts skilled in therapeutic endoscopy.

# Biliary Colic, Cholecystitis

- see General Surgery, GS52

# Ascending Cholangitis

- see General Surgery, GS54

## Definition
- infection of the biliary tree

## Etiology
- stasis in the biliary tract due to obstruction or stricture (usually from previous cholecystectomy)
- infection originates in the duodenum or spreads hematogenously from the portal vein
- bacteria
  - *E. coli, Klebsiella, Enterobacter, Enterococcus*
  - co-infection with *Bacteroides* and *Clostridia* can occur

### Signs and Symptoms
- Charcot's triad: fever, RUQ pain, jaundice (50-70%)
- Reynolds' pentad in patients with suppurative cholangitis: fever, RUQ pain, jaundice, hypotension, altered mental status

**Charcot's Triad**
- RUQ pain
- Fever
- Jaundice

**Reynolds' Pentad**
- Charcot's triad
- Hypotension
- Altered mental status

### Investigations
- increased WBC
- usually increased ALP and bilirubin, ALT variably elevated
- blood culture
- abdominal U/S: CBD dilation, stones

### Treatment
- most important is drainage, ideally via ERCP; perform by percutaneous biliary or by surgical routes (least often) if ERCP not possible
- antibiotic therapy: broad spectrum to cover Gram-negatives, *Enterococcus*, and anaerobes (especially if CBD manipulation); no clear consensus on antibiotic choice but consider:
  - ampicillin + sulbactam or piperacillin/tazobactam
  - metronidazole + 3rd generation cephalosporin (e.g. ceftriaxone) or fluoroquinolone (e.g. ciprofloxacin or levofloxacin)
  - carbapenem monotherapy (e.g. imipenem or meropenem)

### Prognosis
- good with effective drainage and antibiotics in mild to moderate cases
- high mortality (~50%) in patients with Reynolds pentad

# Pancreas

## Pancreatic Enzyme Abnormalities

### Causes of Increased Serum Amylase
- pancreatic disease
  - pancreatitis, pancreatic duct obstruction (e.g. ampullary cancer), pseudocyst, abscess, ascites, trauma, cancer
- non-pancreatic abdominal disease
  - biliary tract disease, bowel obstruction/ischemia, perforated or penetrating ulcer, ruptured ectopic pregnancy, aneurysm, chronic liver disease, peritonitis
- non-abdominal disease
  - cancer (lung, ovary, esophagus, etc.), salivary gland lesions, bulimia, renal transplant/insufficiency, burns, ketoacidosis
  - macroamylasemia

**Pancreatic Enzymes**

**TALC**
**T**rypsin
**A**mylase
**L**ipase
**C**hymotrypsin

### Causes of Increased Serum Lipase
- pancreatic disease: same as above
- non-pancreatic abdominal disease (mild elevations only): same as above
- non-abdominal disease
  - macrolipasemia
  - renal failure

When serum amylase >5x normal, the cause is almost always pancreatitis or renal disease

## Acute Pancreatitis

### Etiology (most common are alcohol and gallstones)
**I**diopathic: thought to be hypertensive sphincter or microlithiasis
**G**allstones (45%)
**E**thanol (35%)
**T**umours: pancreas, ampulla, choledochocele
**S**corpion stings
**M**icrobiological
- bacterial: *Mycoplasma, Campylobacter*, TB, *M. avium intracellulare, Legionella,* leptospirosis
- viral: mumps, rubella, varicella, viral hepatitis, CMV, EBV, HIV, Coxsackie virus, echovirus, adenovirus
- parasites: ascariasis, clonorchiasis, echinococcosis

**A**utoimmune: SLE, *polyarteritis nodosa* (PAN), Crohn's disease
**S**urgery/trauma
- manipulation of sphincter of Oddi (e.g. ERCP), post-cardiac surgery, blunt trauma to abdomen, penetrating peptic ulcer

**H**yperlipidemia (TG >11.3 mmol/L; >1000 mg/dL), hypercalcemia, hypothermia
**E**mboli or ischemia
**D**rugs/toxins
- azathioprine, mercaptopurine, furosemide, estrogens, methyldopa, H2-blockers, valproic acid, antibiotics, acetaminophen, salicylates, methanol, organophosphates, steroids (controversial)

When thinking about the causes of acute pancreatitis remember: **I GET SMASHED**, but vast majority due to gallstones or ethanol

## Pathophysiology

- activation of proteolytic enzymes within pancreatic cells, starting with trypsin, leading to local and systemic inflammatory response
- in gallstone pancreatitis, this is due to mechanical obstruction of the pancreatic duct by stones
- in ethanol-related pancreatitis, pathogenesis is unknown
- in rare genetic diseases, mutations prevent the physiological breakdown of trypsin required normally to stop proteolysis (e.g. mutant trypsin in hereditary pancreatitis or mutation in SPINK 1 gene, which normally inhibits activated trypsin); may be model for ethanol-related pancreatitis



Gallstones only cause acute pancreatitis (not chronic pancreatitis)

## Pathology

- mild (interstitial)
  - peri-pancreatic fat necrosis
  - interstitial edema
- severe (necrotic)
  - extensive peri-pancreatic and intra-pancreatic fat necrosis
  - parenchymal necrosis and hemorrhage → infection in 60%
  - release of toxic factors into systemic circulation and peritoneal space (causes multi-organ failure)
- severity of clinical features may not always correlate with pathology
- 3 phases
  - local inflammation + necrosis → hypovolemia
  - systemic inflammation in multiple organs, especially in lungs, usually after IV fluids given → pulmonary edema
  - local complications 2 wk after presentation → pancreatic sepsis/abscess

## Signs and Symptoms

- pain: epigastric, noncolicky, constant
- can radiate to back
- may improve when leaning forward (Inglefinger's sign)
- tender rigid abdomen; guarding
- nausea/vomiting
- abdominal distention from paralytic ileus
- fever: chemical, not due to infection
- jaundice: compression or obstruction of bile duct
- Cullen's/Grey-Turner's signs
- tetany: transient hypocalcemia
- hypovolemic shock: can lead to renal failure
- acute respiratory distress syndrome
- coma



**Cullen's Sign**
Periumbilical ecchymosis

**Grey-Turner's Sign**
Flank ecchymosis

## Investigations

- increased serum pancreatic enzymes: amylase, lipase (more specific)
- ALT >150 specific for biliary cause
- increased WBC, glucose, low calcium
- imaging: CT most useful for diagnosis and prognosis
  - x-ray: "sentinel loop" (dilated proximal jejunem), calcification, and "colon cut-off sign" (colonic spasm)
  - U/S: useful for evaluating biliary tree (67% sensitivity, 100% specificity)
  - CT scan with IV contrast: useful for diagnosis and prognosis because contrast seen only in viable pancreatic tissue, non-viable areas can be biopsied percutaneously to differentiate sterile from infected necrosis
  - ERCP or MRCP if cause uncertain, assess for duct stone, pancreatic or ampullary tumour, pancreas divisum



**Increased Amylase**
- Sensitive, not specific

**Increased Lipase**
- Higher sensitivity and specificity
- Stays elevated longer

## Classification

- interstitial edematous vs. necrotizing
- mild, moderate, severe

## Prognosis

- usually a benign, self-limiting course, single or recurrent
- occasionally severe leading to:
  - shock
  - pulmonary edema
  - multi-organ dysfunction syndrome
  - GI ulceration due to stress
  - death
    - numerous scales to describe severity: probably most useful is proportion of pancreas not taking up contrast on CT done 48 h after presentation (necrotic pancreas does not take up the contrast dye)
    - presence of organ failure, particularly organ failure that persists >48 h, is associated with worse outcomes

**Table 24. Collections in Pancreatitis (Revised 2012 Atlanta Classification)**

| | Liquid | Solid |
|---|---|---|
| **Acute** | Acute peripancreatic fluid collection (APFC) | Acute necrotic collection (ANC) |
| **Chronic** | Pancreatic pseudocyst | Walled-off necrosis (WON) |

All of these collections are classified as infected or not infected

### Treatment
- goals (only supportive therapy available)

1. hemodynamic stability
2. analgesia
3. oxygen
4. stop progression of damage (difficult)
5. treat local and systemic complications

- antibiotics controversial except in documented infection (use cephalosporins, imipenem)
- aspirate necrotic areas of pancreas to diagnose infection; drain if infected
- IV fluids (crystalloid or colloid)
  - beware third spacing of fluid, monitor urine output carefully
- NG suction (lets pancreas rest) if vomiting, stomach very dilated
- endoscopic sphincterotomy if severe gallstone pancreatitis (i.e. cholangitis or ongoing obstruction)
- nutritional support: nasojejunal feeding tube or TPN if cannot tolerate enteric feeds
  - recent evidence supports nasogastric enteral (or oral if feasible) feeds
- no benefit: glucagon, atropine, aprotinin, H2-blockers, peritoneal lavage
- follow clinically and CT/ultrasound to exclude complications
- chief role of invasive intervention is to excise necrotic tissue (necrosectomy) in the case of infected pancreatic necrosis (try to delay for >2 wk to allow demarcation between viable and necrotic tissue), better done endoscopically or radiologically, rather than surgically if technically possible

### Late Complications
- pseudocysts: follow if asymptomatic, drain if symptomatic or growing
  - drain: choice of endoscopic, percutaneous under radiological guidance, or surgical
- infected necrosis/abscesses: antibiotics + percutaneous drainage, endoscopic vs. surgical
- bleeding: (1) gastric varices if splenic vein thrombosis, (2) pseudoaneurysm of vessels in areas of necrosis, especially splenic artery, (3) duodenal ulcer related to compression of duodenum by enlarged pancreas
- splenic and portal vein thrombosis: no effective therapy described, anticoagulation not proven, hazardous
- rare: DM, pancreatic duct damage

## Chronic Pancreatitis

### Definition
- irreversible damage to pancreas characterized by

1. pancreatic cell loss (from necrosis)
2. inflammation
3. fibrosis

### Etiology/Pathophysiology
- alcohol (most common)
  - causes a larger proportion (>90%) of chronic pancreatitis than acute pancreatitis
  - changes composition of pancreatic juice (e.g. increases viscosity)
  - decreases pancreatic secretion of pancreatic stone protein (lithostathine), which normally solubilizes calcium salts
    - precipitation of calcium within pancreatic duct results in duct and gland destruction
  - toxic effect on acinar and duct cells – directly or via increasing free radicals
  - acinar cell injury leads to cytokine release, which stimulates pancreatic stellate cells to form collagen (leading to fibrosis)
  - varying degrees of ductular dilatation, strictures, protein plugs, calcification
  - no satisfactory theory to explain why only a minority of individuals with alcohol use disorder develop pancreatitis
  - unusual causes
- cystic fibrosis
- severe protein-calorie malnutrition
- hereditary
- idiopathic

### Signs and Symptoms
- early stages
  - recurrent attacks of severe abdominal pain (upper abdomen and back)
  - chronic painless pancreatitis: 10%
- late stages: occurs in 15% of patients
  - steatorrhea (maldigestion) when >90% of function is lost
  - diabetes, calcification, jaundice, weight loss, pseudocyst, ascites, GI bleed



**When to Call the Surgeon in Acute Pancreatitis? Endoscopic Transgastric vs. Surgical Necrosectomy for Infected Necrotizing Pancreatitis: A Randomized Trial**
JAMA 2012; 307:1053-61
Once it was recognized that severe acute (necrotizing) pancreatitis had a terrible prognosis because of an exuberant inflammatory response leading to multiorgan failure, pancreatectomy was attempted. However, contrary to the expected favourable results, clinical experience has shown that surgical pancreatectomy is usually not helpful, perhaps because once the inflammatory cascade starts, it persists as a self-perpetuating cycle. The problems caused by acute pancreatitis can be thought of a widespread burn initiated by inflammation in the pancreas, but having little do with ongoing problems within the pancreas itself. Studies suggest that the only compelling indication for surgery is infected necrotizing pancreatitis not responding to antibiotics. As predicted, without removal of such infected pancreatic tissue, death is likely from sepsis.
In this recent randomized trial, transgastric necrosectomy, an endoscopic technique that also removes infected necrotic pancreatic tissue, reduced both a composite end-point of major pancreatitis complications (especially new onset organ failure) and the pro-inflammatory response (as measured by serum IL-6 levels) to a greater extent than surgical necrosectomy. Of course, not all necrotic collections are in areas amenable to endoscopic intervention, and the advice of an experienced surgeon should always be welcomed in severe acute pancreatitis, but the role of surgery in this previously considered surgical disease is rapidly diminishing.



**Prophylactic Antibiotics Cannot Reduce Infected Pancreatic Necrosis and Mortality in Acute Necrotizing Pancreatitis: Evidence from a Meta-Analysis of Randomized Controlled Trials**
Am J Gastroenterol 2008;103:104-110
**Purpose**: To review the effectiveness of IV antibiotics on pancreatic necrosis.
**Study Selection**: RCTs comparing antibiotics with placebo or no treatment.
**Results**: Seven trials (n=467) were included. Antibiotics were not statistically superior to controls in reduction of infected necrosis and mortality.
**Conclusion**: Prophylactic antibiotics cannot reduce infected pancreatic necrosis and mortality in patients with acute necrotizing pancreatitis.
**Note**:In practice, the temptation to give antibiotics for pancreatitis is mainly in the setting of a sick patient with fever and suggestive pancreatic necrosis on CT scan. It is difficult to determine whether pancreatic necrosis has become infected without aspiration biopsy (see Curr Gastroenterol Rep 2009;11:104-110).



**Symptoms of Chronic Pancreatitis**
- Abdominal pain
- Diabetes
- Steatorrhea

**Etiology** = Almost Always Alcohol

**Treatment**
- Alcohol abstinence
- Pancreatic enzyme replacement
- Analgesics
- Pancreatic resection if ductular blockage

### Investigations
- laboratory
  - increase in serum glucose
  - increase in serum ALP, less commonly bilirubin (jaundice)
  - serum amylase and lipase usually normal
  - stool elastase is low in steatorrhea
- abdominal X-ray: pancreatic calcifications
- U/S or CT: calcification, dilated pancreatic ducts, pseudocyst
- MRCP or ERCP: abnormalities of pancreatic ducts-narrowing and dilatation
- EUS: abnormalities of pancreatic parenchyma and pancreatic ducts, most sensitive test
- 72 h fecal fat test: measures exocrine function
- secretin test: gold standard, measures exocrine function but difficult to perform, unpleasant for patient, expensive
- fecal pancreatic enzyme measurement (elastase-1, chymotrypsin): available only in selected centres

### Treatment
- most common problem is pain, difficult to control
- general management
  - complete abstinence from alcohol
  - enzyme replacement may help pain by resting pancreas via negative feedback
  - analgesics
  - celiac ganglion blocks
  - time: pain decreases with time as pancreas "burns out"
- endoscopy: sphincterotomy, stent if duct dilated, remove stones from pancreatic duct
- surgery: drain pancreatic duct (pancreaticojejunostomy) if duct dilated (more effective than endoscopy); resect pancreas if duct contracted
- steatorrhea
  - pancreatic enzyme replacement
  - restrict fat, increase carbohydrate and protein (may also decrease pain)
  - neither endoscopy nor surgery can improve pancreatic function

## Autoimmune Pancreatitis

- most commonly presents as a mimicker of pancreatic cancer (pancreatic mass detected because of jaundice ± abdominal pain)

### Investigations
- histology: lymphocyte and plasma cell infiltration of pancreas
- imaging: focal or diffuse enlargement of pancreas on CT or MRI, sausage shaped, low density rim around pancreas
- serology: increased serum IgG4
- other organ involvement: sialadenitis, retroperitoneal fibrosis, biliary duct narrowing, nephritis

### Treatment
- responds to prednisone

# Clinical Nutrition

## Determination of Nutritional Status

### Challenging to differentiate markers of malnutrition from markers of disease
- most important feature in assessing the need for nutritional support is weight loss (expressed as change body mass index [kg/m$^2$])
- Subjective Global Assessment divides nutritional status into A) adequately nourished, B) mild or moderate malnutrition and C) severe malnutritionin in order to identify those who will benefit from nutritional support
- includes weight change in past 6 mo, weight change in past 2 weeks, dietary intake change, current dietary intake, GI symptoms, functional capacity, effect of disease on nutritional requirements and physical examination, including loss of subcutaneous fat/muscles wasting/edema/ascites

**Table 25. Small Bowel Nutrient Absorption**

| | Fe | CHO | Proteins, Lipids $Na^+$, $H_2O$ | Bile Acids | Vit $B_{12}$ |
|---|---|---|---|---|---|
| **Duodenum** | +++ | +++ | +++ | + | |
| **Jejunum** | + | + | ++ | + | + |
| **Ileum** | + | + | ++ | +++ | +++ |

### Determining Nutritional Requirements
- calories: total energy expenditure (TEE) = resting energy expenditure (REE) X stress factor (eg 1.7 for burns) usually works out to be 25-35 kcal/kg depending on how disease affects metabolism, with intravenous nutrition delivered as about 60% carbohydrate, 40% fat. Current trend is to provide fewer calories ("permissive underfeeding"), especially in ICU, to prevent hyperglycemia
- protein: 1-2 g/kg/d, depending on effect of disease on protein metabolism. In disease a greater proportion of energy expenditure comes from protein than in health
- electrolytes, minerals and vitamins also required

### Indications for Aggressive Nutritional Support:
- inability to meet nutritional needs; logical, but convincing evidence from literature not available for ICU and other acute illnesses
- evidence that nutritional support improves outcome available for short bowel syndrome (home TPN), when provided before major abdominal or thoracic surgery if there is substantial malnutrition, before radiation therapy for cancer of esophagus, head and neck, decompensated alcoholic liver disease, pancreatitis (acute and chronic)
- nutritional support at best prevents protein loss but usually no gain

## Enteral Nutrition

### Definition
- enteral nutrition (tube feeding) is a way of providing food through a tube placed in the stomach or the small intestine
- nasogastric (NG), or nasojejunal (NJ) if nutritional support required for brief time; percutaneous endoscopic gastrostomy ("G-tube" or "PEG tube")/percutaneous endoscopic jejunostomy (J-tube) if nutrition support required for more than 1 mo
- tubes can also be placed endoscopically, radiologically or surgically

### Indications
- oral feeding inadequate or contraindicated

**Most Common Indications for Artificial Nutrition Support**
- Preexisting nutritional deprivation
- Anticipated or actual inadequate energy intake by mouth
- Significant multiorgan system disease

### Feeds
- polymeric feeds contain whole protein, carbohydrate, fat as a liquid, with or without fibre
- elemental feeds contain protein as amino acids, carbohydrate as simple sugars, fat content low (therefore high osmolarity)
- specific diets: low carbohydrate/high fat solution for ventilated patients (carbohydrate has a high respiratory quotient so minimizes carbon dioxide production), high energy, low electrolyte solutions for dialysis patients

### Relative Contraindications
- non-functioning gut (e.g. intestinal obstruction, enteroenteral or enterocutaneous fistulae)
- uncontrolled diarrhea
- GI bleeding

### Complications
- aspiration
- diarrhea
- refeeding syndrome (rare): carbohydrate can stimulate excessive insulin release, leading to cellular uptake and low serum levels of phosphate, magnesium, potassium
- overfeeding syndrome (rare): hypertonic dehydration, hyperglycemia, hypercapnea, azotemia (from excess protein)

Whenever possible, enteral nutrition is ALWAYS preferable over parenteral nutrition

## Parenteral Nutrition

### Definition
- parenteral nutrition (PN) is the practice of feeding a person intravenously, bypassing the usual process of eating and digestion

### Indications
- short-term (<1 mo)
  - use whenever GI tract not functioning
  - only situations where PN has been well shown to increase survival are after bone marrow transplant and in short bowel syndrome, some evidence for benefit in gastric cancer, but often used in ICU, perioperatively, and in difficult-to-control sepsis
  - pre-operative: only useful in severely malnourished (e.g. loss of >15% of pre-morbid weight, serum albumin <28 g/L or <2.8 g/dL), and only if given for ≥2 wk
  - renal failure: PN shown to increase rate of recovery; no increase in survival
  - liver disease: branched chain amino acids may shorten duration of encephalopathy; no increase in survival
  - IBD: PN closes fistulae and heals acute exacerbations of mucosal inflammation, but effect is transient (EN is equally effective)

- some evidence for efficacy, but convincing data not available for:
  - radiation/chemotherapy-induced enteritis
  - AIDS with wasting diarrhea
  - severe acute pancreatitis
- long-term (>1 mo): can be given at home
  - severe untreatable small bowel disease (e.g. radiation enteritis, extensive CD, high output fistulae)
  - following surgical resection of >70% of small bowel (e.g. small bowel infarction)
  - severe motility diseases (e.g. scleroderma affecting bowel)

### Relative Contraindications
- functional GI tract for enteral nutrition
- active infection; at least until appropriate antibiotic coverage
- inadequate venous access; triple-lumen central venous lines usually prevent this problem

### Complications of PN
- sepsis: most serious of the common complications
- mechanical pneumothorax from insertion of central line, catheter migration and thrombosis, air embolus
- metabolic: congestive heart failure, hyperglycemia, gallstones, cholestasis

### Enteral Nutrition vs. Parenteral Nutrition
- fewer serious complications (especially sepsis) with enteral nutrition
- nutritional requirements for enterally administered nutrition better understood
- can supply gut-specific fuels such as glutamine and short chain fatty acids with enteral nutrition
- nutrients in the intestinal lumen prevent atrophy of the gut and pancreas
- enteral nutrition prevents gallstones by stimulating gallbladder motility
- enteral nutrition much less expensive



Hypomagnesemia may be an initial sign of short bowel syndrome in patients who have undergone surgical bowel resection



**Enteral vs. Parenteral Nutrition for Acute Pancreatitis**
Cochrane DB of Syst Rev 2010;1:CD002837
**Purpose**: Compare EN vs. TPN on mortality, morbidity, and hospital stay in patients with pancreatitis.
**Study Selection**: RCTs of TPN vs. EN in pancreatitis.
**Results**: Eight trials (n=348) were included. Enteral nutrition decreases RR of death (0.50), multiple organ failure (0.55), infection (0.39), and other local complications (0.70). It also decreased hospital stay by 2.37 d.
**Conclusion**: EN reduces mortality, organ failure, infections, and length of hospital stay in patients with pancreatitis.

# Common Medications

**Table 26. Common Drugs Prescribed in Gastroenterology**

| Class | Generic Drug Name | Trade Name | Dosing | Mechanism of Action | Indications | Contraindications | Side Effects |
|---|---|---|---|---|---|---|---|
| **Proton Pump Inhibitors** ($H^+/K^+$-ATPase inhibitors) | omeprazole | Losec®/Prilosec® | 20 mg PO OD | Inhibits gastric enzymes $H^+/K^+$-ATPase (proton pump) | Duodenal ulcer, gastric ulcer, NSAID-associated gastric and duodenal ulcers, reflux esophagitis, symptomatic GERD, dyspepsia, Zollinger-Ellison syndrome, eradication of *H. pylori* (combined with antibiotics) | Hypersensitivity to drug | Dizziness, headache, flatulence, abdominal pain, nausea, rash, increased risk of osteoporotic fracture (secondary to impaired calcium absorption) |
| | lansoprazole or dexlansoprazole | Prevacid® Dexilant® | Oral therapy: lansoprazole 15-30 mg OD (before breakfast), dexlansoprazole 30-60 mg OD (does not need to be taken before breakfast) | Same as above | Same as above | Same as above | Same as above |
| | pantoprazole | Pantoloc® Protonix® | 40 mg PO OD for UGIB: 80 mg IV bolus then 8 mg/h infusion | Same as above | Same as above and UGIB | Same as above | Same as above |
| | rabeprazole | Pariet®/Aciphex® | 40 mg PO OD | Same as above | Same as above | Same as above | Same as above |
| | esomeprazole | Nexium® | 20-40 mg PO OD | Same as above | Same as above | Same as above | Same as above |
| **Histamine H2-Receptor Antagonists** | ranitidine | Zantac® | 300 mg PO OD or 150 mg bid<br>IV therapy: 50 mg q8h (but tachyphylaxis a problem) | Inhibits gastric histamine H2-receptors | Duodenal ulcer, gastric ulcer, NSAID-associated gastric and duodenal ulcers, ulcer prophylaxis, reflux esophagitis, symptomatic GERD; not useful for acute GI bleeds | Hypersensitivity to drug | Confusion, dizziness, headache, arrhythmias, constipation, nausea, agranulocytosis, pancytopenia, depression |
| | famotidine | Pepcid® | Oral therapy: duodenal/gastric ulcers: 40 mg qhs<br>GERD: 20 mg bid<br>IV therapy: 20 mg bid | Same as above | Same as above | Same as above | Same as above |
| **Stool Softener** | docusate sodium | Colace® | 100-400 mg PO OD, divided in 1-4 doses | Promotes incorporation of water into stool | Relief of constipation | Presence of abdominal pain, fever, nausea/vomiting | Throat irritation, abdominal cramps, rashes |
| **Osmotic Laxatives** | lactulose | Lactulose Constulose® | Constipation: 15-30 mL PO OD to bid<br>Encephalopathy: 15-30 mL bid to qid | Poorly absorbed in GI tract and is broken down by colonic bacteria into lactic acid in the colon, increases osmotic colonic contents, increases stool volume | Chronic constipation, prevention, and treatment of portal-systemic encephalopathy | Patients who require a low galactose diet | Flatulence, intestinal cramps, nausea, diarrhea if excessive dosage |
| | PEG3350 | Lax-a-day® RestoraLAX Golytely® | Constipation: 17 g powder dissolved in 4-8 oz liquid PO OD | Osmotic agent causes water retention in stool and promotes frequency of stool | Relief of constipation<br>Colonoscopy prep | Hypersensitivity to drug | Abdominal distension, pain, anal pain, thirst, nausea, rigor, tonic-clonic seizures (rare) |
| | magnesium hydroxide | Milk of Magnesia/Pedia-Lax® | Constipation (adult): 400 mg/5 mL: 30-60 mL PO qhs | Osmotic retention of fluid which distends the colon and increases peristaltic activity | Relief of constipation | Patients with myasthenia gravis or other neuromuscular disease<br>Renal impairment | Abdominal pain, vomiting, diarrhea |

**Table 26. Common Drugs Prescribed in Gastroenterology** (continued)

| Class | Generic Drug Name | Trade Name | Dosing | Mechanism of Action | Indications | Contraindications | Side Effects |
|---|---|---|---|---|---|---|---|
| **Stimulant Laxatives** | senna | Senokot® | Tablets: 1-4 PO qhs<br>Syrup: 10-15 mL PO qhs | Induce peristalsis in lower colon | Constipation | Patients with acute abdomen | Abdominal cramps, discolouration of breast milk, urine, feces, melanosis coli and atonic colon from prolonged use (controversial) |
| | bisacodyl | Bisacodyl® | 5-30 mg PO OD (start at 10 mg for bowel preparation) | Enteric nerve stimulation and local contact-induced secretory effects<br>Colonic movements | Constipation<br>Preparation of bowel for procedure | GI obstruction<br>Gastroenteritis | Abdominal colic, abdominal discomfort, proctitis (with suppository use), diarrhea |
| **Bulk Laxatives** | psyllium | Metamucil | Start at one heaping tablespoon daily | Increases stool bulk → water retention in stool | Constipation | Hypersensitivity to drug<br>GI obstruction | GI obstruction, diarrhea, constipation, abdominal cramps |
| **Guanylate Cyclase C Agonist** | linaclotide | Constella | 75-145 ug once daily | Opens water channels in bowel epithelial cells to add water to stool | Chronic constipation<br>Irritable bowel syndrome-constipation | Children | Diarrhea |
| **Antidiarrheal Agents** | loperamide | Imodium® | Acute diarrhea: 4 mg PO initially, followed by 2 mg after each unformed stool | Acts as antidiarrheal viacholinergic, noncholingeric, opiate, and nonopiate receptor-medicated mechanisms; decreases activity of myenteric plexus | Adjunctive therapy for acute non-specific diarrhea, chronic diarrhea associated with IBD and for reducing the volume of discharge for ileostomies, colostomies, and other intestinal resections | Children <2 yr, known hypersensitivity to drug, acute dysentery characterized by blood in stools and fever, acute ulcerative colitis or pseudomembranous colitis associated with broad-spectrum antibiotics | Abdominal pain or discomfort, drowsiness or dizziness, tiredness, dry mouth, N/V, hypersensitivity reaction |
| | diphenoxylate/ atropine | Lomotil® | 5 mg PO tid to qid | Inhibits GI propulsion via direct action on smooth muscle, resulting in a decrease in peristaltic action and increase in transit time | Adjunctive therapy for diarrhea, as above | Hypersensitivity to diphenoxylate or atropine, jaundice, pseudomembranous enterocolitis, diarrhea caused by enterotoxin producing bacteria | Dizziness, drowsiness, insomnia, headache, N/V, cramps, allergic reaction |
| | eluxadoline | Viberzil | 75-100 mg bid | Bowel opioid modulator | Irritable bowel syndrome<br>Diarrhea | Pancreatic disease Excess alcohol, gallstones or other biliary disease | Pancreatocbiliary pain including sphincter of Oddi dysfunction |
| **Anti-Emetics** | dimenhydrinate | Gravol® | 25-50 mg PO/IV/IM q4-6h prn | Competitive H1 receptor antagonist in GI tract, blood vessels, and respiratory tract. Blocks chemoreceptor trigger zone. Diminishes vestibular simulation and disrupts labyrinthine function through central anticholinergic action | Motion sickness, radiation sickness, postoperative vomiting, and drug-induced nausea/vomiting | Hypersensitivity to drug | Xerostomia, sedation |
| | prochlorperazine | Stemetil® | 5-10 mg PO/IV/IM bid-tid prn | D1, D2 receptor antagonist in chemoreceptor trigger zone and α adrenergic and anti-cholinergic effects<br>Depresses reticular activating system (RAS) affecting emesis | Post-operative N/V, antipsychotic, anxiety | Hypersensitivity to drug | Dystonia, extrapyramidal symptoms (EPS), seizure, neuroleptic malignant syndrome (NMS) (rarely) |
| | metoclopramide | Maxeran® | 10 mg IV/IM q2-3h pm, 10-15 mg PO qid (30 min before meals and qhs) | Dopamine and 5-HT receptor antagonist in chemoreceptor trigger zone. Enhances response to ACh in upper GI tract, enhancing motility and gastric emptying. Increases LES tone | GERD, diabetic gastroparesis, post-operative and chemotherapy induced N/V, migraines, constipation | Hypersensitivity to drug, GI obstruction, perforation, hemorrhage, pheochromocytoma, seizures, and EPS | Restlessness, drowsiness, dizziness, fatigue, EPS, some rare serious side effects include NMS, agranulocytosis |
| | ondansetron | Zofran® | Depends on procedure, generally 8-16 mg PO | Selective 5HT3 receptor antagonist in central chemoreceptor trigger zone and peripherally on vagus nerve | N/V caused by cancer chemotherapy and radiation therapy; multiple off label uses, including gastroenteritis N/V | Morphine, hypersensitivity to drug | Constipation, diarrhea, increased liver enzymes, headache, fatigue, malaise, cardiac dysrhythmia |
| | granisetron | Kytril® | 1 mg PO bid (for nausea from chemotherapy/radiation) | Same as above | N/V caused by cancer chemotherapy and radiation therapy | Same as above | Constipation, prolonged QT interval (rarely) |
| **IBD Agents** | mesalamine | Pentasa®<br>Salofalk®<br>Asacol®<br>Mesasal® | CD: 1 g PO tid/qid<br>Active UC: 1 g PO qid<br>Maintenance UC: 1.6 g PO divided doses daily also as suppositories and enemas | 5-ASA: Blocks arachidonic acid metabolism to prostaglandins and leukotrienes | IBD | Hypersensitivity to mesalamine salicylates; Asacol contains phthalate, potential urogenital teratogenicity for male fetus | Abdominal pain, constipation, arthralgia, headache |
| | sulfasalazine | Salazopyrin® | 3-4 g/d PO in divided doses | Compound composed of 5-ASA bound to sulfapyridine, hydrolysis by intestinal bacteria releases 5-ASA, the active component | Colonic disease | Hypersensitivity to sulfasalazine, sulfa drugs, salicylates; intestinal or urinary obstruction, porphyria | Rash, loss of appetite, N/V, headache, oligospermia (reversible) |
| | prednisone | | 20-40 mg PO OD for acute exacerbation | Anti-inflammatory | Mod-severe CD and UC | | Complications of steroid therapy |

**Table 26. Common Drugs Prescribed in Gastroenterology** (continued)

| Class | Generic Drug Name | Trade Name | Dosing | Mechanism of Action | Indications | Contraindications | Side Effects |
|---|---|---|---|---|---|---|---|
| **Immuno-suppressive Agents** | 6-mercaptopurine (6-MP) | Purinethol® | CD: 1.5 mg/kg/d PO | Immunosuppressive | IBD: active inflammation and to maintain remission | Hypersensitivity to mercaptopurine, prior resistance to mercaptopurine or thioguanine, history of treatment with alkylating agents, hypersensitivity to azathioprine, pregnancy | Pancreatitis, bone marrow suppression, increased risk of cancer |
| | azathioprine | Azasan® Imuran® | IBD: 2-3 mg/kg/d PO | Same as above | Same as above | Same as above | Same as above |
| **Biologics** | infliximab | Remicade® | 5-10 mg/kg IV over 2 h | Monoclonal antibody to TNFα | Medically refractory CD | Heart failure, moderate to severe, doses >5 mg/kg | Reported cases of reactivated TB, PCP, lymphoma, other infections Other TNFα share similar serious side-effects |
| | adalimumab | Humira® | CD induction: four 40 mg SC on day 1, then 80 mg 2 wk later (day 15)<br>CD maintenance: 40 mg every other wk beginning day 29 | Monoclonal antibody to TNFα | Medically refractory CD or poor response to infliximab | Hypersensitivity to adalimumab<br>Severe infection<br>Moderate-to-severe heart failure | Headaches, skin rashes, upper respiratory tract infection |
| | golimumab | Simponi® | RA: 2 mg/kg at wk 0, 4 and then every 8 wk thereafter (use with methotrexate)<br>UC induction: 200 mg SC at wk 0, then 100 mg at wk 2<br>UC maintenance: 50 mg every 4 wk | Monoclonal antibody to TNFα | Active ankylosing spondylitis<br>Psoriatic arthritis<br>Moderate-to-severe active RA (combined with methotrexate)<br>UC: medically refractory UC | Hypersensitivity to golimumab or latex<br>Severe infection<br>Moderate-to-severe heart failure | |
| | vedolizumab | Entyvio | CD/UC: 300 mg at 0, 2, 6 wk and then every 8 wk thereafter | Monoclonal antibody to α4β7 integrin | Medically refractory CD/UC, including other TNFα inhibitors and corticosteroids | Hypersensitivity to vedolizumab | Infections, liver injury, and progressive multifocal leukoencephalopathy |
| | tofactinib | Xeljanz | 5-10 mg bid | JAK inhibitor | Ulcerative colitis | TB, hepatitis B | Infections |
| **Antibiotics** | rifaximin | Zaxine | 550 mg bid or tid | Non-absorable antibiotic, affects dysbiosis of microbiome | Hepatic encephalopathy<br>Non-constipation irritable bowel syndrome<br>Traveller's diarrhea | nil | nil |

# Landmark Gastroenterology Trials

| Trial | Reference | Results |
|---|---|---|
| MELD score as a predictor of death in chronic liver disease | Gastroenterology 2003;124:91-6 | MELD score can be applied for allocation of donor livers as it accurately predicts 3 mo mortality in patients with chronic liver failure |
| Infliximab, azathioprine, or combination for Crohn's disease | NEJM 2010;362:1383-95 | In moderate-severe Crohn's disease, infliximab + azathioprine was more likely to result in corticosteroid-free remission than infliximab monotherapy. Infliximab monotherapy was more effective than azathioprine monotherapy. Similar results have been reported for ulcerative colitis (Gastroenterology 2014; 146:392-400) |
| Enteral versus parenteral nutrition for acute pancreatitis | Cochrane DB Syst Rev 2010;1:CD002837 | For acute pancreatitis, no trial was convincing alone, but in aggregate, enteral feeds via nasogastric tube is preferable to either no feeding or parenteral nutrition |
| Rifaximin treatment in hepatic encephalopathy | NEJM 2010;362:1071-81 | The most convincing of several articles establishing this non-absorbable antibiotic as the treatment of choice for hepatic encephalopathy for maintaining remission from hepatic encephalopathy and reducing hospitalization associated with the disease |
| Adenoma detection rate and risk of colorectal cancer and death | NEJM 2014;370:1298-1306 | A high miss rate for colorectal cancers has been suggested, chiefly in the right colon. This study demonstrates a method of assessing the competence of endoscopists in detecting cancers using adenoma detection rate (the proportion of colonoscopic exams in which a physician detects one or more adenomas) as a surrogate marker. Adenoma detection rate was associated with lower risk of interval colorectal cancer and has launched quality assurance programs for screening colonoscopies |
| Prednisolone or pentoxifylline for alcoholic hepatitis | NEJM 2015;372:1619-28 | For alcoholic hepatitis, prednisolone improved survival when the Maddrey's discriminant function >32, but the benefit did not reach statistical significance and pentoxifylline was of no advantage at all. Other studies had shown some benefit with pentoxifylline, but this study was the most definitive |

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# GS General Surgery and Thoracic Surgery

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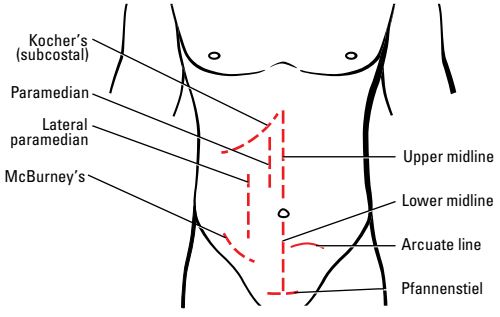
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# Acronyms

| | |
|---|---|
| 5-FU | 5-fluorouracil |
| AAA | abdominal aortic aneurysm |
| ABG | arterial blood gas |
| ABI | ankle brachial index |
| ALND | axillary lymph node dissection |
| ALP | alkaline phosphatase |
| APR | abdominoperineal resection |
| ARDS | acute respiratory distress syndrome |
| ATN | acute tubular necrosis |
| BRBPR | bright red blood per rectum |
| BCS | breast conserving surgery |
| CBD | common bile duct |
| CEA | carcinoembryonic antigen |
| CF | cystic fibrosis |
| CHD | common hepatic duct |
| CHF | congestive heart failure |
| CRC | colorectal cancer |
| CVA | costovertebral angle |
| CVP | central venous pressure |
| DCIS | ductal carcinoma in situ |
| DIC | disseminated intravascular coagulation |
| DM | diabetes meliitus |
| DPL | diagnostic peritoneal lavage |
| DRE | digital rectal exam |
| EBL | estimated blood loss |
| ERCP | endoscopic retrograde cholangiopancreatography |
| EUA | examination under anesthesia |
| EUS | endoscopic ultrasound |
| FAP | familial adenomatous polyposis |
| FAST | focused abdominal sonography for trauma |
| FNA | fine needle aspiration |
| FNH | focal nodular hyperplasia |
| FOBT | fecal occult blood test |
| GERD | gastroesophageal reflux disease |
| GI | gastrointestinal |
| GIST | gastrointestinal stromal tumour |
| GU | genitourinary |
| HCC | hepatocellular carcinoma |
| HDGC | hereditary diffuse gastric carcinoma |
| HIDA | hepatobiliary imino-diacetic acid |
| HNPCC | hereditary nonpolyposis colorectal cancer |
| I&D | incision and drainage |
| IBD | irritable bowel disease |
| IPAH | idiopathic pulmonary arterial hypertension |
| IPF | idiopathic pulmonary fibrosis |
| IUGR | Intrauterine growth restriction |
| IVC | inferior vena cava |
| IVIG | Intravenous immune globulin |
| LAR | low anterior resection |
| LBO | large bowel obstruction |
| LCIS | lobular carcinoma in situ |
| LES | lower esophageal sphincter |
| LGIB | lower gastrointestinal bleed |
| LMWH | low molecular weight heparin |
| LVRS | lung volume reduction surgery |
| MALT | mucosa-associated lymphoid tissue |
| MBP | mechanical bowel preparation |
| MEN | multiple endocrine neoplasia |
| MIBG | metaiodobenzylguanidine |
| MIS | minimally invasive surgery |
| MRCP | magnetic resonance cholangiopancreatography |
| MSAFP | maternal serum alpha-fetoprotein |
| N/V | nausea/vomiting |
| NET | neuroendocrine tumour |
| NGT | nasogastric tube |
| NPO | nothing by mouth |
| NS | normal saline |
| OCP | oral contraceptive pill |
| OGD | oesophagogastroduodenoscopy |
| PMN | polymorphonuclear neutrophils |
| POD | post-operative day |
| PPI | proton pump inhibitor |
| PTC | percutaneous transhepatic cholangiography |
| PTT | partial thromboplastin time |
| PUD | peptic ulcer disease |
| RAI | radioactive iodine |
| SBO | small bowel obstruction |
| SBFT | small bowel follow-through |
| SCC | squamous cell carcinoma |
| SIADH | syndrome of inappropriate anti-diuretic hormone |
| SMA | superior mesenteric artery |
| SMV | superior mesenteric vein |
| SNLB | sentinel lymph node biopsy |
| TED | thromboembolic deterrent |
| TEE | transesophageal echocardiogram |
| TTE | transthoracic echocardiogram |
| UC | ulcerative colitis |
| UGI | upper gastrointestinal series |
| UGIB | upper gastrointestinal bleed |
| URTI | upper respiratory tract infection |
| VATS | video-assisted thorascopic surgery |
| VIP | vasoactive intestinal |
| VTE | venous thromboembolism |

# Basic Anatomy Review




| | |
|---|---|
| **Kocher's (subcostal)** | Access to RUQ or LUQ contents i.e. gallbladder, spleen |
| **Upper Midline** | Access to stomach, duodenum, gallbladder, liver, transverse colon |
| **Paramedian** | Can make similar incision in each quadrant for access to each quadrant's contents<br>Not commonly used<br>Post-operative ventral hernias common |
| **Lateral Paramedian** | Incision made at outer 1/3 - medial 2/3 border of rectus<br>Modification of paramedian but with lower risk of dehiscence or ventral hernia<br>Not commonly used |
| **Lower Midline** | Access to pelvic organs, sigmoid colon, and rectum |
| **Pfannenstiel** | Suprapubic incision for access to pelvic cavity |
| **McBurney's** | Access to appendix |

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**Figure 1. Abdominal incisions**

### Lateral Abdominal Wall Layers and their Continuous Spermatic and Scrotal Structures (superficial to deep)

1. skin (epidermis, dermis, subcutaneous fat)
2. superficial fascia
   - Camper's fascia (fatty) → Dartos muscle/fascia
   - Scarpa's fascia (membranous) → Colles' superficial perineal fascia
3. muscle (see Figure 2 and Figure 3)
   - external oblique → inguinal ligament → external spermatic fascia and fascia lata
   - internal oblique → cremasteric muscle/fascia
   - transversus abdominis → posterior inguinal wall
4. transversalis fascia → internal spermatic fascia
5. preperitoneal fat
6. peritoneum → tunica vaginalis

### Midline Abdominal Wall Layers (superficial to deep)

1. skin
2. superficial fascia
3. rectus abdominis muscle: in rectus sheath, divided by linea alba (see Figure 3)
   - above arcuate line (midway between symphysis pubis and umbilicus)
     - anterior rectus sheath = external oblique aponeurosis and anterior leaf of internal oblique aponeurosis
     - posterior rectus sheath = posterior leaf of internal oblique aponeurosis and transversus abdominis aponeurosis
   - below arcuate line
     - aponeuroses of external oblique, internal oblique, transversus abdominis all pass in front of rectus abdominis
4. arteries: superior epigastric (branch of internal thoracic), inferior epigastric (branch of external iliac); both arteries anastomose and lie behind the rectus muscle (superficial to posterior rectus sheath above arcuate line)
5. transversalis fascia
6. peritoneum

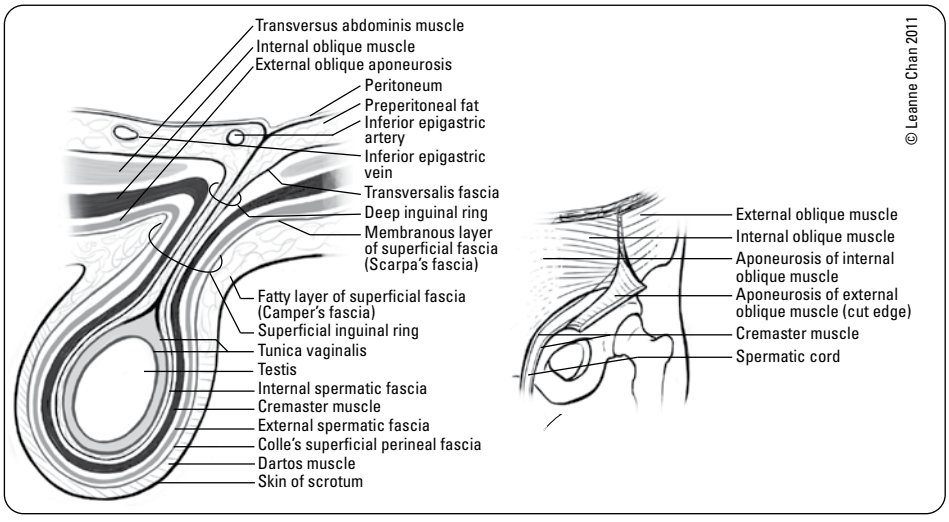



**Figure 2. Continuity of the abdominal wall with layers of the scrotum and spermatic cord**

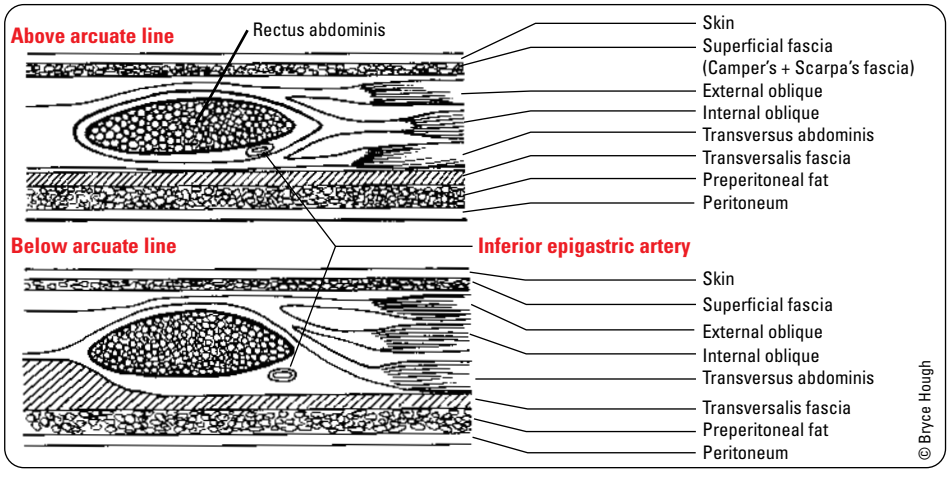



**Figure 3. Midline cross-section of abdominal wall**

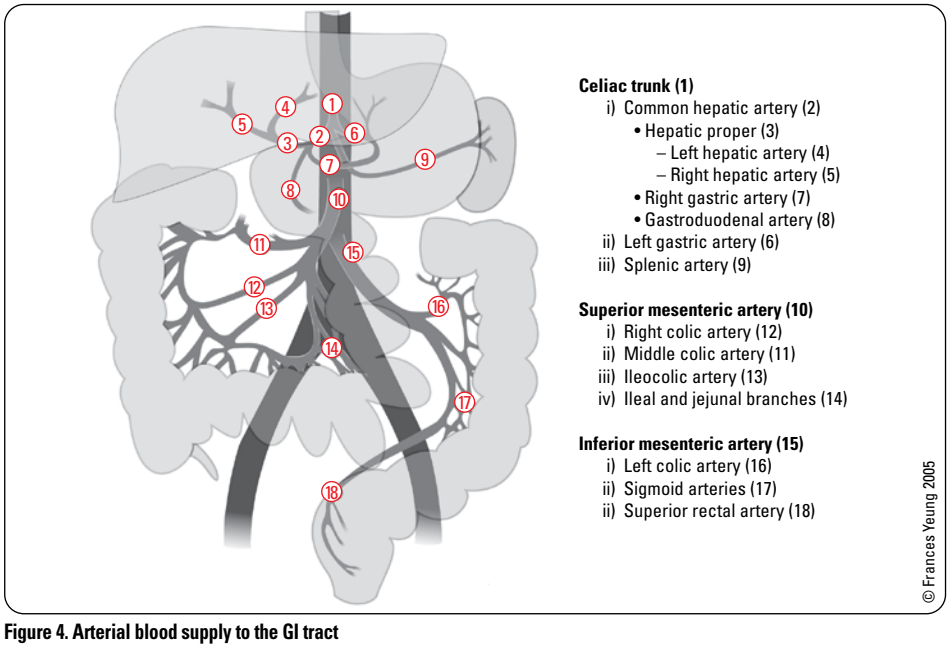
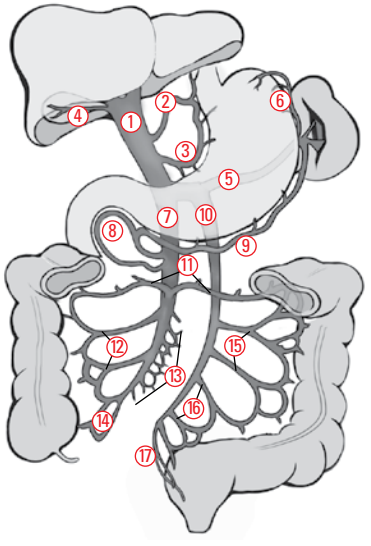



**Figure 4. Arterial blood supply to the GI tract**

### Venous Flow




**Portal vein (1)**

**Superior mesenteric vein (7)**
- i) Ileal and jejunal veins (13)
- ii) Ileocolic vein (14)
- iii) Right colic vein (12)
- iv) Middle colic vein (11)
- v) Pancreaticoduodenal vein (8)
- vi) Right gastroepiploic vein (9)

**Splenic vein (5)**
- i) Inferior mesenteric vein (10) (superior rectal vein until crossing common iliac vessels)
  - Left colic veins (15)
  - Sigmoid veins (16)
  - Superior rectal veins (17)
- ii) Pancreatic veins
- iii) Left gastroepiploic vein
- iv) Short gastric veins (6)

**Left gastric (coronary) vein (2)**

**Right gastric vein (3)**

**Cystic vein (4)**

**Paraumbilical vein – (within round ligament, not shown)**

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**Figure 5. Venous drainage of the GI tract**

| Organ | Arterial Blood Supply |
|---|---|
| **Liver** | Left and right hepatic (branches of hepatic proper) |
| **Spleen** | Splenic |
| **Gallbladder** | Cystic (branch of right hepatic) |
| **Stomach** | 1. Lesser curvature: right and left gastric<br>2. Greater curvature: right (branch of gastroduodenal) and left (branch of splenic) gastroepiploic<br>3. Fundus: short gastrics (branches of splenic) |
| **Duodenum** | 1. Gastroduodenal<br>2. Pancreaticoduodenals (superior branch of gastroduodenal, inferior branch of superior mesenteric) |
| **Pancreas** | 1. Pancreatic branches of splenic<br>2. Pancreaticoduodenals |
| **Small intestine** | Superior mesenteric branches: jejunal, ileal, ileocolic |
| **Large intestine** | 1. Superior mesenteric branches: right colic, middle colic<br>2. Inferior mesenteric branches: left colic, sigmoid, superior rectal |

# Differential Diagnoses of Common Presentations

## Acute Abdominal Pain

- acute abdomen = severe abdominal pain of acute onset and requires urgent medical attention
- in patients with acute abdominal pain, the first diagnoses that you should consider are those requiring potential urgent surgical intervention
- two main patterns constituting urgent general surgery referrals are peritonitis and obstruction

**Table 1. Differential Diagnosis of Acute Abdominal Pain**

| RUQ | RLQ |
|---|---|
| **Hepatobiliary** | **Gastrointestinal** |
| Biliary colic | Appendicitis* |
| Cholecystitis* | Crohn's disease |
| Cholangitis | Tuberculosis of the ileocecal junction |
| CBD obstruction (e.g stone, tumour) | Cecal tumour |
| Hepatitis (includes perihepatitis/Fitz-Hugh-Curtis syndrome) | Intussusception |
| Portal vein thrombosis | Mesenteric lymphadenitis (*Yersinia*) |
| Budd-Chiari syndrome | Cecal diverticulitis |
| Hepatic abscess/mass | Cecal volvulus* |
| Right subphrenic abscess* | Hernia: femoral, inguinal obstruction, Amyand's (and resulting cecal distention) |
| **Gastrointestinal** | **Gynecological** |
| Pancreatitis | See 'suprapubic' |
| Presentation of gastric, duodenal, or pancreatic pathology | **Genitourinary** |
| Hepatic flexure pathology (e.g. CRC, subcostal incisional hernia) | See 'suprapubic' |
| **Genitourinary** | **Extraperitoneal** |
| Nephrolithiasis* | Abdominal wall hematoma/abscess |
| Pyelonephritis | Psoas abscess |
| Renal: mass, ischemia, trauma | |
| **Cardiopulmonary** | |
| RLL pneumonia | |
| Effusion/empyema | |
| CHF (causing hepatic congestion and R pleural effusion) | |
| MI | |
| Pericarditis | |
| Pleuritis | |
| **Miscellaneous** | |
| Herpes zoster | |
| Trauma | |
| Costochondritis (Infectious*) | |

**In All Patients Presenting with an Acute Abdomen, Order the Following:**

**KEY TESTS FOR SPECIFIC DIAGNOSIS**
- ALP, ALT, AST, bilirubin
- Lipase/ amylase
- Urinalysis
- β-hCG (in women of childbearing age)
- Troponins
- Lactate

**KEY TESTS FOR OR PREPARATION**
- CBC, electrolytes, creatinine, glucose
- INR/PTT
- CXR (if history of cardiac or pulmonary disease)
- ECG if clinically indicated by history or if >69 yr and no risk factors

Note: Choosing Wisely does not recommend routine preoperative blood work for ambulatory/elective surgery

**Types of Peritonitis**
- Primary peritonitis: spontaneous without clear etiology
- Secondary peritonitis: due to a perforated viscus
- Tertiary peritonitis: recurrent secondary peritonitis more often with resistant organisms

**Localization of Pain**

Most digestive tract pain is perceived in the midline because of bilaterally symmetric innervation; kidney, ureter, ovary, or somatically innervated structures are more likely to cause lateralized pain

Parietal peritoneum: supplied by somatic sensory nerves of body wall. Pain is sharp and well-localized.

Visceral peritoneum: supplied by autonomic sensory fibres. Pain is colicky and poorly-localized.

**Table 1. Differential Diagnosis of Acute Abdominal Pain** (continued)

| LUQ | LLQ |
|---|---|
| **Pancreatic**<br>Pancreatitis (acute vs. chronic)<br>Pancreatic pseudocyst<br>Pancreatic tumours* | **Gastrointestinal**<br>Diverticulitis*<br>Diverticulosis<br>Colon/sigmoid/rectal cancer<br>Fecal impaction<br>Proctitis (e.g. ulcerative colitis, infectious; i.e. *gonococcus* or *Chlamydia*)<br>Sigmoid volvulus* |
| **Gastrointestinal**<br>Gastritis<br>PUD<br>Splenic flexure pathology (e.g. CRC, ischemia) | Hernia (incarcerated/strangulated*) |
| **Splenic**<br>Splenic infarct/abscess*<br>Splenomegaly<br>Splenic rupture*<br>Splenic artery aneurysm | **Gynecological**<br>See 'suprapubic' |
| **Cardiopulmonary (see RUQ and Epigastric)** | **Genitourinary**<br>See 'suprapubic' |
| **Genitourinary (see RUQ)** | **Extraperitoneal**<br>Abdominal wall hematoma/abscess*<br>Psoas abscess |
| | See Gynecology, Urology, Respirology, and Cardiology and Cardiac Surgery for further details regarding respective etiologies of acute abdominal pain |

| EPIGASTRIC | SUPRAPUBIC | DIFFUSE |
|---|---|---|
| **Cardiac**<br>Aortic dissection/ruptured AAA*<br>MI<br>Pericarditis | **Gastrointestinal (see RLQ/LLQ)**<br>Acute appendicitis*<br>IBD | **Gastrointestinal**<br>Peritonitis*<br>Early appendicitis, perforated appendicitis*<br>Mesenteric ischemia*<br>Gastroenteritis/colitis<br>Constipation<br>Bowel obstruction*<br>Pancreatitis<br>Inflammatory bowel disease<br>Irritable bowel syndrome<br>Ogilvie's syndrome |
| Gastrointestinal<br>Gastritis<br>GERD/esophagitis<br>PUD<br>Pancreatitis<br>Mallory-Weiss tear | **Gynecological**<br>Ectopic pregnancy*<br>Pelvic inflammatory disease<br>Endometriosis<br>Threatened/incomplete abortion*<br>Hydrosalpinx/salpingitis<br>Ovarian torsion*<br>Hemorrhagic fibroid<br>Tubo-ovarian abscess<br>Gynecological tumours | **Cardiovascular/Hematological**<br>Aortic dissection/ruptured AAA*<br>Sickle cell crisis |
| | **Genitourinary**<br>Cystitis (infectious, hemorrhagic)<br>Hydroureter/urinary colic<br>Epididymitis<br>Testicular torsion*<br>Acute urinary retention | **Genitourinary/Gynecological**<br>Perforated ectopic pregnancy*<br>Pelvic inflammatory disease<br>Acute urinary retention |
| | **Extraperitoneal**<br>Rectus sheath hematoma | **Endocrinological**<br>Carcinoid syndrome*<br>Diabetic ketoacidosis<br>Addisonian crisis<br>Hypercalcemia |
| | | **Other**<br>Lead poisoning<br>Tertiary syphilis |

*indicated need for urgent surgical evaluation

**Referred Pain**
- Biliary colic: to right shoulder or scapula
- Renal colic: to groin
- Appendicitis: periumbilical to right lower quadrant (RLQ)
- Pancreatitis: to back
- Ruptured aortic aneurysm: to back or flank
- Perforated ulcer: to RLQ (right paracolic gutter)
- Hip pain: to groin
- Ovarian Torsion: to flank or groin

**Most Common Presentations of Surgical Pain**
- Sudden onset with rigid abdomen = perforated viscus
- Pain out of proportion to physical findings = ischemic bowel
- Vague pain that subsequently localizes = appendicitis or other intra-abdominal process that irritates the parietal peritoneum
- Waves of colicky pain = bowel obstruction

**Acute Abdominal Pain Mnemonic**
**A**ppendicitis
**B**iliary Tract Disease
**D**iverticulitis
**O**varian disease
**M**alignancy
**I**ntestinal Obstruction
**N**ephritic Disorders
**A**cute Pancreatitis
**L**iquor/Ethanol

# Abdominal Mass

**Table 2. Differential Diagnosis of Abdominal Mass**

| Right Upper Quadrant (RUQ) | Upper Midline | Left Upper Quadrant (LUQ) |
|---|---|---|
| **Gallbladder**: cholecystitis, cholangiocarcinoma, peri-ampullary malignancy, cholelithiasis<br>**Biliary tract**: Klatskin tumour<br>**Liver**: hepatomegaly, hepatitis, abscess, tumour (hepatocellular carcinoma, metastatic tumour, etc.) | **Pancreas**: pancreatic adenocarcinoma, other pancreatic neoplasm, pseudocyst<br>**Abdominal aorta**: AAA (pulsatile)<br>**GI**: gastric tumour (adenocarcinoma, gastrointestinal stromal tumour, carcinoid tumour), MALT lymphoma | **Spleen**: splenomegaly, tumour, abscess, subcapsular splenic hemorrhage, can also present as RLQ mass if extreme splenomegaly<br>**Stomach**: tumour |
| **Right Lower Quadrant (RLQ)** | **Lower Midline** | **Left Lower Quadrant (LLQ)** |
| **Intestine**: stool, tumour (CRC), mesenteric adenitis, appendicitis, appendiceal phlegmon or other abscess, typhlitis, intussusception, Crohn's inflammation<br>**Ovary**: ectopic pregnancy, cyst (physiological vs. pathological), tumour (serous, mucinous, struma ovarii, germ cell, Krukenberg)<br>**Fallopian tube**: ectopic pregnancy, tubo-ovarian abscess, hydrosalpinx, tumour | **Uterus**: pregnancy, leiomyoma (fibroid), uterine cancer, pyometra, hematometra<br>**GU**: bladder distention, tumour | **Intestine**: stool, tumour, abscess (see RLQ)<br>**Ovary**: see RLQ<br>**Fallopian tube**: see RLQ |

Pancreatitis can look like a surgical abdomen, but is rarely an indication for immediate surgical intervention

# Gastrointestinal Bleeding

• see Gastroenterology, G25

## Indications for Surgery

- failure of medical management
- exsanguinating hemorrhage: hemodynamic instability despite vigorous resuscitation
- recurrent hemorrhage with up to two attempts of endoscopic hemostasis
- prolonged bleeding with transfusion requirement >3 units
- bleeding at rate >1 unit/8 h

## Surgical Management of GI Bleeding

- UGIB
  - bleeding from a source proximal to the ligament of Treitz
  - often presents with hematemesis and melena unless very brisk (then can present with hematochezia)
  - initial management with endoscopy; if fails, then consider surgical management appropriate to etiology
  - PUD accounts for approximately 55% of severe UGIB
- LGIB
  - bleeding from a source distal to the ligament of Treitz
  - often presents with BRBPR unless proximal to transverse colon
  - may occasionally present with melena
  - initial management with colonoscopy to detect and potentially stop source of bleeding
  - 75% of patients will spontaneously stop bleeding, however if bleeding continues barium enema should NOT be performed
  - angiography or RBC scan to determine source as indicated
  - surgery indicated if bleeding is persistent - aimed at resection of area containing source of bleeding
  - obscure bleed may require blind total colectomy if the source is not found

**Table 3. Differential Diagnosis of GI Bleeding**

| Anatomical Source | Etiology | |
|---|---|---|
| **Hematological** | Excess anticoagulation (coumadin, heparin, etc.)<br>Excess antiplatelet (clopidogrel, ASA) | DIC<br>Congenital bleeding disorders |
| **Nose** | Epistaxis | |
| **Esophagus** | Esophageal varices<br>Mallory-Weiss tear<br>Esophagitis | Aorto-esophageal fistula (generally post endovascular aortic repair)*<br>Esophageal cancer |
| **Stomach** | Gastritis<br>Gastric varices<br>Dieulafoy's lesion | Gastric ulcer<br>Gastric cancer* |
| **Duodenum** | Duodenal ulcer<br>Perforated duodenal ulcer* | Duodenal cancer* |
| **Jejunum** | Tumours*<br>Polyps<br>Ulcers | |
| **Ileum and Ileocecal Junction** | Meckel's diverticulum<br>Small bowel obstruction | Crohn's disease*<br>Tuberculosis of ileocecal junction |
| **Large Intestine** | Colorectal cancer*<br>Mesenteric thrombosis/ischemic bowel*<br>Ulcerative colitis* (subtotal colectomy if failure of medical management)<br>Angiodysplasia<br>Diverticulosis (*if bleeding is persistent) | Crohn's disease (less frequently presents with bleeding)*<br>Pancolitis (infectious, chemotherapy, or radiation induced)<br>Bleeding post-gastrointestinal anastomosis |
| **Sigmoid** | Diverticulosis (*if bleeding is persistent)<br>Sigmoid cancer*<br>Bleeding post-polypectomy | Polyps (*if not amenable to colonoscopic polypectomy)<br>Inflammatory bowel disease (IBD) |
| **Rectum and Anus** | Hemorrhoids<br>Fissures<br>Rectal cancer*<br>Anal varices | Polyps (*if not amenable to colonoscopic polypectomy)<br>Crohn's or ulcerative colitis*<br>Solitary rectal ulcer syndrome |

*Managed surgically in most cases

**Indications for Urgent Operation**

**IHOP**
**I**schemia
**H**emorrhage
**O**bstruction
**P**erforation

**Overt bleeding**: obvious hematemesis, hematochezia or melena per rectum (i.e. visible to naked eye)
**Occult bleeding**: bleeding per rectum is not obvious to naked eye (e.g. positive guaiac FOBT)
**Obscure bleeding**: bleeding with no identifiable source after colonoscopy and endoscopy (source usually in small bowel). Can be either overt or occult

**Transfusion Strategies for Acute Upper Gastrointestinal Bleeding**
NEJM 2013;368:11-21
Recent study by Villanueva et al., demonstrates that a restrictive transfusion strategy (transfusion with hemoglobin below 70 g/L) significantly improves outcomes in patients with acute UGIB, compared to a liberal transfusion strategy (transfusion with hemoglobin below 90 g/L). Refer to study for details.

# Jaundice

• see Gastroenterology, G43

**Biochemical Signs for Differentiating Jaundice**
**Hepatocellular**: Elevated bilirubin + elevated ALT/AST
**Cholestatic**: Elevated bilirubin + elevated ALP/GGT ± duct dilatation upon biliary U/S
**Hemolysis**: ↓ haptoglobin ↑ LDH

Note: cholestatic jaundice is often surgical

# Pre-Operative Preparations

## Considerations

- informed consent (see Ethical, Legal, and Organizational Medicine, ELOM7)
- screening questionnaire to determine risk factors e.g. age, exercise capacity, medication use, allergies
- consider pre-operative anesthesia, medicine consult as indicated to optimize patient status
- NPO according to fasting guidelines (see Anesthesia and Perioperative Medicine, A6)
- IV – balanced crystalloid at maintenance rate (4:2:1 rule for pediatrics, roughly 100-125 cc/h for adults): normal saline or Ringer's lactate (RL most common); bolus to catch up on estimated losses including losses from bowel prep
  - appropriate use of fluids perioperatively decreases risk of cardiorespiratory complications
- patient's regular medications included with the exception of hypoglycemic agents, diuretics and ACEI
- patients on steroids may require stress dose coverage
- anticoagulation/antiplatelet medication must be managed to decrease surgical bleeding but not put patient at risk for increased thrombotic events (e.g. Bridging: switching from warfarin to LMWH, easier to start/stop as needed)
- prophylactic antibiotics depending on wound class (immediately/within 1 h prior to incision): cefazolin (Ancef®) ± metronidazole (Flagyl®) for contaminated cases
- role of MBP: Current evidence suggests that use of MBP pre-operatively has no impact on post-operative complications and therefore routine use of MBP for non-LAR elective colorectal surgery is not recommended
  - MBP is still frequently used for left-sided colonic surgery (i.e. sigmoid and rectum) to facilitate bowel manipulation and colorectal anastomoses
- consider VTE prophylaxis for all inpatient surgery (LMWH or heparin)
- only hold VTE prophylaxis if epidural is expected
- smoking cessation and weight loss pre-operatively can significantly decrease post-operative complications
- infection: delay elective surgery until infection controlled, including respiratory infection (particularly in asthma patients)

## Investigations

- see Anesthesia and Perioperative Medicine, A2
- routine pre-operative laboratory investigations for elective procedures should be selective
  - only ASA class and surgical risk have been found to independently predict post-operative adverse effects
- blood components: group and screen or cross and type depending on procedure
- CBC, electrolytes, creatinine
- INR/PT, PTT
- CXR (PA and lateral) for patients with history of cardiac or pulmonary disease
- ECG as indicated by history or if >69 yr and no risk factors
- β-hCG testing in all women of reproductive age

## Drains

- NGT
  - indications: gastric decompression, analysis of gastric contents, irrigation/dilution of gastric contents, feeding, if necessary
  - 2 types: NGT (for drainage or feeding) and Dobhoff (for feeding only)
  - insertion should be done in stages with x-ray protocol to avoid injury
  - contraindications: suspected basal skull fracture, obstruction of nasal passages, esophageal stricture, esophageal varices
- Foley catheter with urometer
  - indications: to accurately monitor urine output, decompression of bladder, relieve obstruction, rapidly expanding suprapubic mass
  - contraindications: suspected urethral injury, and difficult insertion of catheter

# Surgical Complications

- general principles in preventing complications during the post-operative period include:
  - frequent examination of the patient (daily or more) and their wound
  - removal of surgical tubes as soon as possible (e.g. Foley catheters and surgical drains)
  - early ambulation
  - monitor fluid balance and electrolytes
  - analgesia - enough to adequately address pain, but not excessive (minimize opioids)
  - skillful nursing care

# Post-Operative Fever

- fever does not necessarily imply infection particularly in the first 24-48 h post-operative
- fever may not be present or is blunted if patient is receiving chemotherapy, glucocorticoids, or other immunosuppression

**Bilirubin Levels**

| | Prehepatic | Intrahepatic | Posthepatic |
|---|---|---|---|
| **Serum Bilirubin** | | | |
| Indirect | ↑ | ↑ | N |
| Direct | N | ↑ | ↑ |
| **Urine** | | | |
| Urobilinogen | ↑ | ↑ | – |
| Bilirubin | – | + | + |
| **Fecal** | | | |
| Urobilinogen | ↑ | ↑ | – |

In patients with liver disease and an acute abdomen, spontaneous bacterial peritonitis must be ruled out

**Surgical Emergencies: Take an AMPLE History**
**A**llergies
**M**edications
**P**ast medical/surgical history (including anesthesia and bleeding disorders)
**L**ast meal
**E**vents (HPI)

**Best Practice in General Surgery (BPIGS)**
http://www.bpigs.ca/
BPIGS is a University of Toronto initiative with the goal of standardizing care in general surgery. This link contains EBM based guidelines which have been implemented by consensus within all Toronto teaching hospitals. This is a highly recommended source for the most up-to-date pre-operative and general treatment guidelines

**Mechanical Bowel Preparation Strategies: A Clinical Practice Guideline developed by the University of Toronto's Best Practice in Surgery**
Informed by: Can J Surg 2010;53:385–395
14 RCTs (5071 participants), 8 meta-analyses
1. All open/laparoscopic colorectal procedures (excluding LARs ± diverting stoma)
   - No MBP
   - No dietary restrictions before NPO
   - Fleet enema for left colon anastomoses with transrectal stapling
2. Open/laparoscopic LAR ± diverting stoma
   - MBP
   - No dietary restrictions before MBP; clear fluids after MBP complete

**Drain Size**
Measured by the unit French:
French = diameter (mm) x 3

- timing of fever may help identify cause
  - hours after surgery – POD #1
    - inflammatory reaction in response to trauma from surgery (physiologic); unlikely to be infectious (unless necrotizing fasciitis or another severe infection)
    - reaction to blood products received during surgery
    - malignant hyperthermia
  - POD #1-2 (acute)
    - atelectasis (most common cause of fever on POD #1)
    - early wound infection (especially *Clostridium*, Group A *Streptococcus* – feel for crepitus and look for "dishwater" drainage)
    - aspiration pneumonitis
    - other: Addisonian crisis, thyroid storm, and transfusion reaction
  - POD #3-7: likely infectious
    - UTI, surgical site infection, IV site/line infection, septic thrombophlebitis, and leakage at bowel anastomosis (tachycardia, hypotension, oliguria, and abdominal pain)
  - POD #8+
    - intra-abdominal abscess, DVT/PE (can be anytime post-operative, most commonly POD #8-10, may occur earlier but recognition is often delayed), and drug fever
    - other: cholecystitis, peri-rectal abscess, URTI, infected seroma/biloma/hematoma, parotitis, *C. difficile* colitis, and endocarditis

### Treatment
- treat primary cause
- antipyrexia (e.g. acetaminophen)

**Pre- and Post-Operative Orders**

**ADDAVIDS**
**A**dmit to ward X under Dr. Y
**D**iagnosis
**D**iet
**A**ctivity
**V**itals (q4h from ED and post-operative is standard)
**I**V, Investigations, Ins and Outs
**D**rugs, Dressings, Drains
**S**pecial procedures

**5 Ws of Post-Operative Fever**
**W**ind POD #1-2 (pulmonary – atelectasis, pneumonia)
**W**ater POD #3-5 (urine – UTI)
**W**ound POD #5-8 (wound infection - if earlier think streptococcal or clostridial infection)
**W**alk POD #8+ (thrombosis – DVT/PE)
**W**onder drugs POD #1+ (drug)

**Drugs – 7 As**
**A**nalgesia
**A**nti-emetic
**A**nticoagulation
**A**ntibiotics
**A**nxiolytics
**A**nticonstipation
**A**ll other patient meds (home meds, stress dose steroids, and β-blockers)

**Approach to the Critically Ill Surgical/ Trauma Patient**

**ABC, I'M FINE**
**ABC**
**I**V: 2 large bore IVs with NS, wide open
**M**onitors: $O_2$ sat, ECG, BP
**F**oley catheter to measure urine output
**I**nvestigations: blood work
**N**GT if indicated
"**Ex**" rays (abdomen 3 views, CXR), other imaging – only when stable

# Wound/Incisional Complications

## WOUND CARE (see Plastic Surgery, PL8)
- can shower POD #2-3 after epithelialization of wound (or earlier depending on dressing)
- dressings can be removed POD #2 and left uncovered if dry
- examine wound if wet dressing, signs of infection (fever, tachycardia, and pain)
- skin sutures and staples can be removed POD #7-10
  - exceptions: incision crosses crease (groin), closed under tension, in extremities (hand) or patient factors (elderly, corticosteroid use, or immunosuppressed) removed POD #14, earlier if signs of infection
- negative pressure dressings consist of foam and suction, promote granulation
  - ideal for large (grafted sites) or non-healing wounds (irradiated skin, or ulcer)

## DRAINS
- drains may be placed selectively at the time of surgery to prevent fluid accumulation (blood, pus, serum, bile, and urine)
  - can be used to assess quantity of third space fluid accumulation post-operatively
- potential route of infection; to decrease risk of wound infection bring out through separate incision (vs. operative wound) and remove as soon as possible
- types of drains
  - open (e.g. Penrose), higher risk of infection
  - closed: 1) Gravity drainage (e.g. Foley catheter); 2) Underwater-seal drainage system (e.g. chest tube); 3) Suction drainage (e.g. Jackson-Pratt)
  - sump (e.g. NGT)
- monitor drain outputs daily
- drains should be removed once drainage is minimal (usually <30-50 cc/24 h)
- drains do not guarantee that the patient will not form a collection of fluid
- ridged drains can erode through internal structures, and excessive suction can cause necrosis
- evidence does not support routine post-operative drainage of abdominal cavity

## SURGICAL SITE INFECTION

### Etiology
- *S. aureus, E. coli, Enterococcus, Streptococcus* spp., *Clostridium* spp.

### Risk Factors

**Table 4. Procedures and Their Impact on Surgical Site Infection**

| Classification | Clean | Clean-Contaminated | Contaminated | Dirty/Infected |
|---|---|---|---|---|
| **Definition** | Incision under sterile conditions; nontraumatic; no entrance of hollow organ | Incision under sterile conditions; ENTRANCE of hollow viscus; no evidence of active infection; minimal contamination | Incision under sterile conditions; MAJOR contamination of wound during procedure (i.e. gross spillage of stool, infection in biliary, respiratory, or GU systems) | Established infection present before wound is made in skin |
| **Example** | Hernia repair | Routine cholecystectomy; colon resection | Bowel obstruction with enterotomy and spillage of contents; necrotic bowel resection; fresh traumatic wounds | Appendiceal abscess; traumatic wound with contaminated devitalized tissue; perforated viscus |
| **Infection Rate** | <2% | 3-4% | 7-10% | 30-40% |
| **Wound Closure** | Primary closure | Primary closure | Often secondary closure | Secondary closure |

- patient characteristics
  - age, DM, steroids, immunosuppression, obesity, burn, malnutrition, patient with other infections, traumatic wound, radiation, and chemotherapy
- other factors
  - prolonged pre-operative hospitalization, reduced blood flow, break in sterile technique, multiple antibiotics, hematoma, seroma, foreign bodies (drains, sutures, grafts), skin preparation, hypoxemia, and hypothermia

### Prophylaxis
- pre-operative antibiotics for most surgeries (cefazolin ± metronidazole or if β-lactam allergy, clindamycin ± gentamycin)
  - within 1 h pre-incision; can redose at 1-2 half-lives (~q4-8h) in the OR
  - not required for low risk elective thyroidectomy, cholecystectomy, hemorrhoidectomy, fistulotomy, and sphincterotomy for fissure
  - some evidence suggests role in breast surgery
- reserve post-operative antibiotics for treatment of suspected or documented intra-abdominal infection
- normothermia (maintain patient temperature 36-38°C during OR)
- hyperoxygenation (consider $FiO_2$ of 80% in OR)
- chlorhexidine-alcohol wash of surgical site
- hair removal should not be performed unless necessary; if so, clipping superior to shaving
- consider delayed primary closure of incision for contaminated wounds
- use sterile closing tray for laparotomy

### Clinical Feature
- typically fever POD #5-8 (*Streptococcus* and *Clostridium* can present in 24 h)
- localized pain, blanchable erythema, induration, purulent discharge, and warmth
- complications: fistula, sinus tracts, sepsis, abscess, suppressed wound healing, superinfection, spreading infection to myonecrosis or fascial necrosis (necrotizing fasciitis), wound dehiscence, evisceration, and hernia

### Treatment
- examination of the wound: inspect, compress adjacent areas, swab drainage for C&S and Gram stain
- re-open affected part of incision, drain, pack, heal by secondary intention in most cases
- for deeper or necrotizing infections, debride necrotic and non-viable tissue
- antibiotics and demarcation of erythema only if cellulitis or immunodeficiency

## WOUND HEMORRHAGE/HEMATOMA

### Risk Factors
- anticoagulant therapy, coagulopathies, thrombocytopenia, DIC, severe liver disease, myeloproliferative disorders, severe arterial HTN, and severe cough
- more common with transverse incisions through muscle, due to cutting of muscle
- more clinically relevant in small working spaces such as breast surgery or thyroid surgery

### Clinical Features
- pain, swelling, discolouration of wound edges, and leakage
- rapidly expanding neck hematoma can compromise airway and is a surgical emergency: consider having a suture kit at bedside in all neck surgery in the event of having to open the wound emergently (most important treatment in this case is to protect the airway with intubation)

### Treatment
- pressure dressing
- open drainage ± wound packing (large hematoma only)
- if significant bleeding, may need to re-operate to find source (often do not find a discrete source)

## SEROMA
- fluid collection other than pus or blood
- secondary to transection of lymph vessels
- delays healing
- increased infection risk if drained

### Treatment
- observation
- consider pressure dressing ± needle drainage (this may increase infection risk)
- if significant may need to re-operate

## WOUND DEHISCENCE
- disruption of a wound that was primarily closed, causing loss of barrier of skin or fascia

### Risk Factors
- local: technical failure of closure, technical errors including excessive tension on the wound, increased intra-abdominal pressure (e.g. COPD, ileus, bowel obstruction), hematoma, infection, poor blood supply, radiation, patient not fully paralyzed while closing, and transverse incision

| Complication | Laboratory/Imaging Tests |
|---|---|
| **Wound Complication** | wound culture, CBC, CT scan |
| **Fever** | CBC, electrolytes, glucose, creatinine, BUN, UA, CXR urine/ blood/sputum and wound culture if applicable |
| **Respiratory Distress** | EKG, echo, CXR, ABG, CT-angiography of the chest |
| **AKI/Oliguria** | electrolytes, glucose, creatinine, BUN, UA with microscopy, urine electrolytes, EKG, renal ultrasound |
| **Hypotension** | CBC, electrolytes, glucose, creatinine, BUN, lactate, ABG, ACTH stimulation testing and cortisol level; coagulation studies |
| **Ileus** | electrolytes, glucose, creatinine, BUN, abdominal x-ray |
| **Stress ulcer** | CBC, upper endoscopy |



**Pre-Operative Skin Antiseptics for Preventing Surgical Wound Infections After Clean Surgery**
Cochrane DB Syst Rev 2015;4:CD003949
**Purpose**: To determine if pre-operative skin antisepsis prior to clean surgery prevents surgical-site infection (SSI) and compare the effectiveness of other antiseptics.
**Methods**: Systematic review of randomized-controlled trials (RCTs) part of the Cochrane Wounds Group Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL). Main outcome was SSI. Secondary outcomes included quality of life, mortality, and resource use.
**Results**: 13 RCTs (n=2623 patients) were included that made 11 total comparisons between skin antiseptics. A single study found that 0.5% chlorhexidine solution in methylated spirits was significantly superior in preventing SSIs after clean surgery compared to alcohol based povidone iodine solution. No other statistically significant differences were found.
**Conclusions**: Further research is warranted to determine the effectiveness of one antiseptic over the others at preventing SSI post clean surgery.



**Systemic Review and Meta-Analysis of Randomized Clinical Trials Comparing Primary vs. Delayed Primary Skin Closure in Contaminated and Dirty Abdominal Incisions**
JAMA Surg 2013;148:779-786
**Purpose**: To compare rates of surgical site infection (SSI) with delayed primary closure (DPC) vs. primary skin closure (PC).
**Results/Conclusions**: 8 RCTs with 623 patients. Most common diagnosis was appendicitis (77.4%). Although there was significant heterogeneity between studies, DPC (2-5 d time to first review) was found to significantly reduce the chance of SSI (OR 0.65, 95% CI 0.40-0.93). Although current trials are poorly designed, DPC may be a simple and cost-effective way of reducing the rates of SSIs following abdominal surgery with contaminated or dirty wounds.

- systemic: male, smoking, malnutrition (hypoalbuminemia, vitamin C deficiency), connective tissue diseases, immunosuppression, pulmonary disease, ascites, poor nutrition, steroids, chemotherapy, obesity, and other (e.g. age, sepsis, and uremia)
- DM alone is not a risk factor

### Clinical Features
- typically POD #1-3 or #7-10; most common presentation sign is serosanguinous drainage from wound
- ± evisceration
- palpation of wound edge: should normally feel a "healing ridge" from abdominal wall closure (raised area of tissue under incision)

### Treatment
- place moist dressing over wound with binder around abdomen and transfer to OR
- may consider conservative management with debridement of fascial and/or skin margins
- evisceration (i.e. 'burst abdomen') is a surgical emergency: take patient for operative re-closure without abdomen binder

## INCISIONAL HERNIA
- defined as either part or all of an abdominal wound in which the fascial edges have separated
- symptoms aggravated by coughing or straining
- smaller fascial defects such as laparoscopic port sites have a higher risk of incarceration
- definitive treatment: surgical repair
  - large hernias that pose little risk of incarceration do not need to be repaired

**Small Bites versus Large Bites for Closure of Abdominal Midline Incisions (Stitch): A Double-Blind, Multicentre, Randomised Controlled Trial**
Lancet 2015;386:1254-1260
**Purpose**: To compare the large bites suture technique with the small bites technique for fascial closure of midline laparotomy incisions.
**Methods**: Randomized controlled trial conducted at ten hospitals in the Netherlands. Patients undergoing elective abdominal surgery randomized (1:1) to small or large bite technique. Primary outcome was incisional hernia occurrence.
**Results**: At one year follow-up, the large bites group had a greater incidence of incisional hernia occurrence than the small bites group (21% vs 13%, respectively). Rates of adverse events did not differ between the groups.
**Conclusion**: Small bites suture technique is superior to the large bites technique for prevention of incisional hernia in midline incisions and is not associated with a higher rate of adverse events.

# Urinary and Renal Complications

## URINARY RETENTION
- may occur after any operation with general anesthesia or more commonly with spinal anesthesia
- more likely in older males with history of benign prostatic hyperplasia, and patients on anticholinergics

### Clinical Feature
- abdominal discomfort, palpable bladder, overflow incontinence, post-void residual urine volume >100 mL

### Treatment
- Foley catheter to rest bladder, then trial of voiding
- often accompanied by an alpha-blocker such as tamsulosin

## OLIGURIA/ANURIA

### Etiology
- prerenal vs. renal vs. postrenal
- most common post-operative cause is prerenal ± ischemic ATN
  - external fluid loss: hemorrhage, dehydration, and diarrhea
  - internal fluid loss: third-spacing due to bowel obstruction, and pancreatitis

### Clinical Feature
- urine output <0.5 cc/kg/h, increasing Cr, and increasing BUN

### Treatment
- according to underlying cause; fluid deficit is treated with crystalloid (NS or RL)

# Post-Operative Dyspnea

- see *Respiratory Complications and Cardiac Complications*, GS12

### Etiology
- respiratory: atelectasis, pneumonia/pneumonitis, pulmonary embolus (PE), ARDS, asthma, and pleural effusion
- cardiac: MI, arrhythmia, and CHF
- inadequate pain control

# Respiratory Complications

## ATELECTASIS
- comprises 90% of post-operative pulmonary complications

### Risk Factors
- COPD, smoking, obesity, and elderly persons
- upper abdominal/thoracic surgery, oversedation, significant post-operative pain, and poor inspiratory effort

### Clinical Features
- low-grade fever on POD #1, tachycardia, crackles, decreased breath sounds, bronchial breathing, and tachypnea

### Treatment
- pre-operative prophylaxis
  - smoking cessation (best if >8 wk pre-operative)
- post-operative prophylaxis
  - incentive spirometry, deep breathing exercise, chest physiotherapy, and intermittent positive-pressure breathing
  - selective NGT decompression after abdominal surgery
  - short-acting neuromuscular blocking agents
  - minimize use of respiratory depressive drugs, appropriate pain control, and early ambulation

## PNEUMONIA/PNEUMONITIS
- may be secondary to aspiration of gastric contents during anesthetic induction or extubation, causing a chemical pneumonitis

### Risk Factors
- aspiration: general anesthetic, decreased LOC, GERD, full stomach, bowel/gastric outlet obstruction + non-functioning NGT, pregnancy, and seizure disorder
- non-aspiration: atelectasis, immobility, and pre-existing respiratory disease

### Clinical Features
- productive cough, and fever
- tachycardia, cyanosis, respiratory failure, and decreased LOC
- CXR: pulmonary infiltrate

### Treatment
- prophylaxis: see atelectasis prophylaxis, pre-operative NPO/NGT, and rapid sequence anesthetic induction
- immediate removal of debris and fluid from airway
- consider endotracheal intubation and flexible bronchoscopic aspiration
- empiric IV antibiotics to cover oral nosocomial aerobes and anaerobes (e.g. piperacillin-tazobactam, cefepimemetronidazole)

## PULMONARY EMBOLUS

### Clinical Features
- unilateral leg swelling and pain (DVT as a source of PE), sudden onset dyspnea, pleuritic chest pain, tachycardia, and fever
- most commonly POD #8-10, but can occur anytime post-operatively, even after discharge
- diagnosis made by Chest CT scan usually

### Treatment
- initial treatment: IV heparin or subcutaneous LMWH, bridging to therapeutic anticoagulation is required for a minimum of 3 mo (usually 6 mo); for patients with cancer, or other risk factors for hypercoagulability, the duration of anticoagulation may be longer
- Greenfield (IVC) filter if contraindications to anticoagulation helps prevent worsening of PE
- prophylaxis: subcutaneous heparin (5000 U bid) or LMWH, compression stockings (TED™ Hose), and sequential compression devices

## PULMONARY EDEMA



New onset "asthma" and wheezing in the elderly is cardiogenic until proven otherwise

### Etiology
- cardiogenic vs. noncardiogenic
- circulatory overload: excess volume replacement, LV failure, shift of fluid from peripheral to pulmonary vascular bed, negative airway pressure, and alveolar injury due to toxins (e.g. ARDS)
  - more common with pre-existing cardiac disease
- negative pressure pulmonary edema due to inspiratory efforts against a closed glottis upon awakening from general anesthesia

### Clinical Features
- shortness of breath, crackles at lung bases, and CXR abnormal

### Treatment (LMNOP)
- **L**asix
- **M**orphine (decreases symptoms of dyspnea, venodilator, and afterload reduction)
- **N**itrates (venodilator)
- **O**xygen + non-invasive ventilation
- **P**osition (sit patient up)

### RESPIRATORY FAILURE

#### Clinical Features
- dyspnea, cyanosis, and evidence of obstructive lung disease
- earliest manifestations – tachypnea and hypoxemia (RR >25, $pO_2$ <60)
- pulmonary edema, and unexplained decrease in $SaO_2$

#### Treatment
- ABCs, $O_2$, ± positive pressure ventilation, and intubation
- bronchodilators, and diuretics to treat CHF
- adequate blood pressure to maintain pulmonary perfusion
- if these measures fail to keep $PaO_2$ >60, consider ARDS (see Respirology, R26)

## Cardiac Complications

- abnormal ECGs common in post-operative period (compare to pre-operative ECG)
- common arrhythmias: supraventricular tachycardia, atrial fibrillation (secondary to fluid overload, PE, and MI)

### MYOCARDIAL INFARCTION
- see Cardiology and Cardiac Surgery, C39
- surgery increases risk of MI
- incidence
  - 0.5% in previously asymptomatic men >50 yr old
  - 40-fold increase in men >50 yr old with previous MI

#### Risk Factors
- pre-operative HTN, CHF
- previous MI (highest risk ≤6 mo, but risk never returns to baseline)
- increased age
- intra-operative hypotension
- operations >3 h
- angina

#### Clinical Features
- majority of cases on day of operation or POD #3-4 (shifting of third space fluid back into intravascular compartment)
- often silent without chest pain, may only present with new-onset CHF (dyspnea), arrhythmias, and hypotension

## Intra-Abdominal Abscess

#### Definition
- collection of pus walled-off from rest of peritoneal cavity by inflammatory adhesions and viscera

#### Etiology
- usually polymicrobial: Gram-negative bacteria, and anaerobes
  - consider Gram-positives if coexisting cellulitis

#### Risk Factors
- emergency surgery, and contaminated OR
- GI surgery with anastomotic leak
- poor healing risk factors (DM, poor nutrition, etc.)
- may occur POD #3 after laparotomy when third space fluid re-distribution occurs

#### Clinical Features
- persistent spiking fever, dull pain, and weight loss
- mass difficult to palpate
- peritoneal signs if abscess perforation and secondary peritonitis
- leukocytosis or leukopenia (immunocompromised, and elderly)
- co-existing effusion (pleural effusion with subphrenic abscess)
- common sites: pelvis, Morrison's pouch (space between kidney and liver), subphrenic, paracolic gutters, lesser sac, peri-appendiceal, post-surgical anastomosis, diverticular, and psoas

#### Investigations
- CBC, blood cultures x2
- CT ± IV and water-soluble contrast
- DRE (pelvic abscess)

#### Treatment
- drain placement by interventional radiology (preferred), laparoscopy, and open drainage
- subsequent antibiotic coverage; ceftriaxone + metronidazole or piperacilin-tazobactam (Pip-Tazo)

# Paralytic Ileus

- see *Bowel Obstruction*, GS26

# Delirium

- see Psychiatry, PS22 and Neurology, N20

# Thoracic Surgery

## Hiatus Hernia

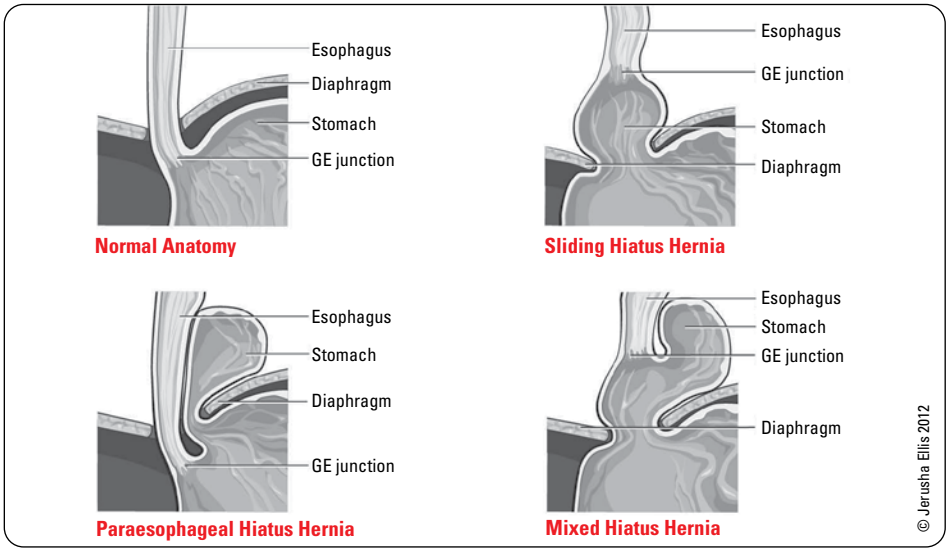



**Figure 6. Types of hiatus hernia:** Type I: Sliding (GE junction above the level of the diaphgram) Type II: Paraesophageal (GE junction below the diaphgram, fundus rolls past it) Type III: Mixed and Type IV: Massive (not shown) (containing another intraabodminal organ: bowel/spleen/etc.)

**Differential Diagnosis of Hiatus Hernia**

| GI Causes | Non-GI Causes |
|---|---|
| Cholelithiasis | MI |
| Diverticulitis | Angina |
| Peptic ulcer | Pericarditis |
| Achalasia | |
| Pancreatitis | |
| GERD | |
| Gastritis | |

### SLIDING HIATUS HERNIA (TYPE I)

- herniation of both the stomach and the gastroesophageal (GE) junction into thorax
- 90% of esophageal hernias

#### Risk Factors

- age
- increased intra-abdominal pressure (e.g. obesity, pregnancy, coughing, and heavy lifting)
- smoking

#### Clinical Features

- majority are asymptomatic
- hernias frequently associated with GERD due to decreased competence of LES

#### Complications

- most common symptom is GERD
- other complications are rare and are related to reflux
- esophagitis (dysphagia, and heartburn)
- consequences of esophagitis (peptic stricture, Barrett's esophagus, and esophageal carcinoma)
- extra-esophageal complications (aspiration pneumonitis/pneumonia, bronchospasm, cough, and laryngitis)

#### Investigations

- barium swallow, endoscopy (esophago-gastroscopy), or esophageal manometry (technique for measuring LES pressure)
- 24 h esophageal pH monitoring to quantify reflux
- endoscopy with biopsy to document type and extent of tissue damage and rule out esophagitis, Barrett's esophagus, and cancer

#### Treatment

- lifestyle modification
  - stop smoking, weight loss, elevate head of bed, no meals <3 h prior to sleeping, smaller and more frequent meals, avoid alcohol, coffee, mint, and fat

- medical
  - antacid, H2-antagonist, PPI, prokinetic agent
- surgical (<15%)
  - consider if: volume regurgitation, patient unwilling or unable to stay on PPI indefinitely, suboptimal medical therapy, complications of GERD such as pharyngitis, esophageal stricture, recurrent nocturnal aspiration, Barrett's esophagus, patient preference
  - hiatus hernia repair and fundoplication
- anti-reflux procedure (usually laparoscopic)
  - fundus of stomach is wrapped around the lower esophagus and sutured in place
  - 360 degree wrap: Nissen Fundoplication, 270 degree wrap: Toupet, 180 degree wrap: Dor
  - complications: dysphagia, gas bloat, diarrhea, recurrence
  - dysphagia and gas bloat may be less with partial fundoplications (Toupet/Dor)
  - 90% success rate for alleviating GERD

### PARAESOPHAGEAL HIATUS HERNIA (TYPE II)
- see Figure 6
- herniation of all or part of the stomach through the esophageal hiatus into the thorax with an undisplaced GE junction
- least common esophageal hernia (<10%)

#### Clinical Features
- usually asymptomatic due to normal GE junction
- pressure sensation in lower chest, dysphagia

#### Complications
- hemorrhage, incarceration, strangulation (gastric volvulus), obstruction, gastric stasis ulcer (Cameron's lesion – causes Fe-deficiency anemia)

### MIXED HIATUS HERNIA (TYPE III)
- see Figure 6
- second most common type of hernia – combination of types I and II
- includes giant hernias or intrathoracic stomach
- rare incidence of gastric volvulus (Borschadt's Triad: chest pain, retching, inability to pass NG tube)
- majority present with long-standing Fe-deficiency anemia of unknown etiology
- symptoms commonly include reflux or heartburn
- most common symptoms: abnormal postprandial fullness after normal-sized meal, chest pain or retrosternal discomfort (gastric angina), and bloating
- can present with gastric outlet obstruction or gastric necrosis secondary to strangulation in the setting of gastric volvulus

#### Treatment
- surgery to address symptoms or treat/prevent complications
- reduce hernia and excise hernia sac, repair defect at hiatus, and anti-reflux procedure (e.g. Nissen fundoplication)
- may consider suturing stomach to anterior abdominal wall (gastropexy)
- in very elderly patients at high surgical risk consider PEG (percutaneous endoscopic gastrostomy) to anchor the stomach in the abdomen

### TYPE IV HERNIA
- herniation of stomach and other abdominal organs into thorax: colon, spleen, and small bowel
- Fe-deficiency anemia is common

## Esophageal Perforation



**Boerhaave's syndrome:** transmural esophageal perforation
**Mallory-Weiss tear:** non-transmural esophageal tear (partial thickness tear)
Both are associated with forceful emesis



**6Ss of SCC**
**S**moking
**S**pirits (alcohol)
**S**eeds (betel nut)
**S**calding (hot liquid)
**S**trictures
**S**ack (diverticula)

#### Etiology
- iatrogenic (most common)
  - endoscopic, dilatation, biopsy, intubation, operative, and NGT placement (rare)
- barogenic
  - trauma
  - repeated, forceful vomiting (Boerhaave's syndrome)
  - other: convulsions, defecation, or labour (rare)
- ingestion injury
  - foreign body or corrosive substance
- carcinoma

#### Clinical Features
- neck or chest pain
- fever, tachycardia, hypotension, dyspnea, and respiratory compromise
- subcutaneous emphysema, pneumothorax, pleural effusion, and hematemesis

#### Investigations
- CXR: pneumothorax, pneumomediastinum, pleural effusion, subdiaphragmatic air, and widened mediastinum

- CT chest: pneumomediastinum, pleural effusion, pneumothorax, contrast in the chest, and subcutaneous emphysema
- upper GI swallow study with water soluble contrast
  - if negative then perform with diluted barium: contrast extravasation
  - barium swallow is gold standard to diagnose esophageal perforation
  - CT esophagram useful to rule out large leaks

### Treatment
- supportive if rupture is contained (see sidebar for Cameron's criteria)
- surgical
  - <24 h from perforation
    - primary closure of a healthy esophagus with buttressed intercostal muscle flap or resection of diseased esophagus
  - >24 h from perforation or non-viable wound edges
    - diversion and exclusion followed by delayed reconstruction (i.e. esophagostomy proximally, close esophagus distally, and gastrostomy/jejunostomy for decompression/feeding)

### Complications
- sepsis, abscess, fistula, empyema, mediastinitis, and death
- post-operative esophageal leak
- mortality 10-50% dependent on timing of diagnosis

**Cameron's criteria for conservative management of esophageal perforation**
Disruption contained in mediastinum
Barium drains back into esophagus
No signs of sepsis
Minimal symptoms

## Esophageal Carcinoma

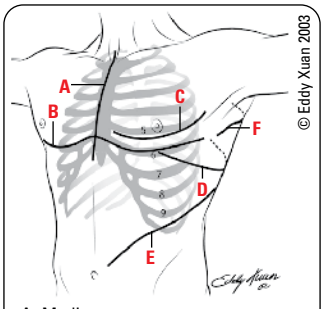
### Epidemiology
- M:F = 3:1
- onset 50-60 yr of age
- upper (20-33%), middle (33%), and lower (33-50%)
- main types
  - most common worldwide: SCC in upper 2/3 of esophagus
  - most common in Western countries: adenocarcinoma in distal 1/3 of esophagus

### Risk Factors
- SCC
  - underlying esophageal disease such as strictures, diverticula, and achalasia
  - smoking, alcohol, and hot liquids
  - more common in black and Asian populations
- adenocarcinoma
  - Barrett's esophagus (most important), smoking, obesity (increased reflux), and GERD
  - more common in Caucasian populations

### Clinical Features
- progressive dysphagia (mechanical): first solids then liquids
- odynophagia then constant pain
- constitutional symptoms
- regurgitation and aspiration (aspiration pneumonia)
- hematemesis and anemia
- direct, hematogenous, or lymphatic spread
  - trachea (coughing), recurrent laryngeal nerves (hoarseness, vocal paralysis), aortic, liver, lung, bone, celiac, and mediastinal nodes

### Investigations and Staging
- barium swallow: shows narrowing – suggestive but not diagnostic
- endoscopic biopsy and assess resectability
- both SCC and adenocarcinoma use TNM staging system but have separate stage groupings according to histology
- endoscopic U/S (EUS)
  - visualize local disease
  - regional nodal involvement (number of nodes may be more important than location)
- bronchoscopy ± thoracoscopy
  - rule out airway invasion in tumours of the upper and mid esophagus
- full metastatic workup (CXR, bone scan, CT head, CT chest/abdomen/pelvis, and LFTs, etc.)
- PET scan more sensitive than CT in detecting metastatic disease

### Treatment
- if early stage (non-transmural and without evidence of nodal disease)
  - endoscopic mucosal resection can be considered for early mucosal cancer or high grade dysplasia
  - esophagectomy (transthoracic or trans-hiatal approach) and lymphadenectomy
    - anastomosis in chest or neck
    - stomach most often used for reconstruction; may also use colon
  - adjuvant chemotherapy ± radiation usually recommended for post-operative node-positive disease




A. Median sternotomy
B. Transverse thoracotomy (clam shell)
C. Anterolateral thoracotomy
D. Lateral thoracotomy
E. Thoracoabdominal thoracotomy
F. Posterolateral thoracotomy

**Figure 7. Typical thoracic surgery incisions**

**Standard of Care in 2019:**
1) Pre- and post-operative FLOT chemotherapy for gastric and GE junction adenocarcinoma (docetaxel, oxaliplatin and fluorouracil/leucovorin)
2) Neoadjuvant CROSS chemoradiotherapy for esophageal cancer with squamous histology or mid-body adenocarcinoma (carboplatin and paclitaxel plus radiotherapy)

**Perioperative Chemo(radio)therapy vs. Primary Surgery for Resectable Adenocarcinoma of the Stomach, Gastroesophageal Junction, and Lower Esophagus**
Cochrane DB Syst Rev 2013;5:CD008107
**Study**: Review of RCTs to examine the effect of perioperative chemotherapy for gastroesophageal adenocarcinoma on survival and other clinically relevant outcomes.
**Results/Conclusions**: 14 RCTs, 2422 participants.
1) Perioperative chemotherapy was associated with a significantly longer overall survival (HR 0.81, 95% CI 0.73 to 0.89), a relative survival increase of 19% and an absolute increase of 9%.
2) Tumours of the GE junction showed a more pronounced response to perioperative chemotherapy compared to other sites.
3) Combined chemoradiotherapy was more effective for tumours of the esophagus and GE junction compared to chemotherapy alone.
4) Perioperative chemotherapy was more effective in younger patients and is associated with longer disease-free survival, higher rates of R0 resection, and a more favourable tumour stage upon resection.
5) Resection with negative margins is a strong predictor of survival.

- if locally advanced (locally invasive disease or nodal disease on CT or EUS)
  - multimodal therapy
    - concurrent external beam radiation and chemotherapy (cisplatin and 5-FU)
    - possibility of curative esophagectomy after chemoradiation if disease responds well
  - if unable to tolerate multimodal therapy or if highly advanced disease, consider palliative resection, brachytherapy, or endoscopic dilatation/stenting/laser ablation for palliation
- if present with distant metastatic disease
  - treat with systemic therapy and treat symptoms (esophageal stent)

### Prognosis
- TNM status - usually poor because presentation is usually at advanced stage

### OTHER DISORDERS
- esophageal motor disorders (see Gastroenterology, G8)
- esophageal varices (see Gastroenterology, G29)
- Mallory-Weiss tear (see Gastroenterology, G29)

## Thymoma

### Epidemiology
- rare neoplasms in thymus including both thymoma and thymic carcinoma
- patients between 40 and 60 yr
- M = F

### Risk Factors
- no known risk factors, strong association with myasthenia gravis and other paraneoplastic syndromes

### Clinical Feature
- frequently asymptomatic: incidental finding on imaging
- symptoms related to tumour size and location or myasthenia gravis: chest pain, SOB, cough, and phrenic nerve palsy
- ddx includes intrathoracic goitre, lymphoma, and other anterior mediastinal tumours (see Respirology, R22)

### Investigations
- CT chest (and/or MRI)
- Germ cell tumour markers (β-hCG, alpha fetoprotein), thyroid function, and PFTs

### Treatment
- for patients with resectable disease
  - surgical resection of thymus via median sternotomy or VATS depending on the size
  - ± post-operative radiation based on Masaoka staging
  - Masaoka I: completely encapsulated; II: invasion beyond capsule; III: into another organ; IVa pleural/pericardial mets, IVb hematogeous/lymphatic mets
  - radiation considered for stage II/III disease
- for non-surgical patients
  - multimodal therapy including neoadjuvant or palliative chemotherapy and post-operative chemoradiotherapy if de-bulking procedure feasible

### Prognosis
- depends upon stage of disease and resectability
- generally slow growing tumours and have good prognosis, however thymic carcinomas more aggressive and have poorer prognosis

## Pleura, Lung, and Mediastinum

- see Respirology, R22

## Complicated Effusion

- persistent bacteria in the pleural space but fluid is non-purulent
- neutrophils, pleural fluid acidosis (pH <7.00), and high LDH
- often no bacteria grown since rapidly cleared from pleural space
- fibrin layer leading to loculation of pleural fluid
- treatment: antibiotics depending on Gram stain and chest tube drainage

## Empyema

### Definition
- pus in pleural space or an effusion with organisms seen on a Gram stain or culture (e.g. pleural fluid is grossly purulent)
- positive culture is not required for diagnosis

### Etiology
- contiguous spread from lung infection (most commonly anaerobes) or infection through chest wall (e.g. trauma, surgery)

### Signs and Symptoms
- fever, pleuritic chest pain

### Investigations
- CT chest
- thoracentesis
  - PMNs (lymphocytes in TB) ± visible organisms on Gram stain

### Treatment
- antibiotic therapy for at least 4-6 wk (rarely effective alone)
- complete pleural drainage with chest tube
- if loculated, more difficult to drain – may require surgical drainage with video-assisted thorascopic surgery (VATS), or removal of fibrin coating (surgical or tPA/DNAse) to allow lung re-expansion (decortication)

## Pneumothorax

### Definition
- presence of air in the pleural space

### Pathophysiology
- entry of air into pleural space raises intrapleural pressure causing partial lung deflation

### Etiology
- traumatic: penetrating or non-penetrating chest injuries
- iatrogenic: central venous catheter, thoracentesis, mechanical ventilation with barotrauma
- spontaneous: no history of trauma
  - primary (no underlying lung disease)
    - spontaneous rupture of apical subpleural bleb (packets of air) of lung into pleural space
    - smoker, male, family history, Marfan's syndrome
  - secondary (underlying lung disease)
    - rupture of subpleural bleb which migrates along bronchioalveolar sheath to the mediastinum then to the intrapleural space
    - necrosis of lung tissue adjacent to pleural surface
    - pneumonia, abscess, PCP, lung CA, COPD, CF, TB, LAM, Pulmonary Langerhans cell histiocytosis (PLCH)

### Signs and Symptoms
- can be asymptomatic
- acute-onset pleuritic chest pain, dyspnea
- tachypnea, tachycardia
- tracheal deviation (contralateral deviation in tension pneumothorax)
- ipsilateral diminished chest expansion
- decreased tactile/vocal fremitus
- hyperresonance
- ipsilateral diminished breath sounds

### Investigations
- CXR
  - small: separation of visceral and parietal pleura seen as fine crescentic line parallel to chest wall at apex
  - large: decreased density and decreased volume of lung on side of pneumothorax
  - see Medical Imaging, MI9

### Treatment
- primary spontaneous pneumothorax
  - stable, small (<3 cm), minimal symptoms: observation + $O_2$
  - symptomatic or large (>3 cm): aspiration
  - unstable/tension pneumothorax: needle decompression then chest tube, and VATS if unsuccessful (25-50%)
- secondary spontaneous pneumothorax
  - stable, small (<3 cm), minimal symptoms: observation + $O_2$
  - symptomatic, large, or unstable: chest tube, and VATS if unsuccessful

# Tube Thoracostomy

## Indications

- to drain abnormal large-volume air or fluid collections in the pleural space
  - hemothorax, pleural effusion, chylothorax, and empyema
  - pneumothorax, if:
  - large or progressive
  - patient is on mechanical ventilation
  - bronchopleural fistula
  - tension pneumothorax
- to treat symptomatic and/or recurrent pleural effusion
  - see Respirology, R23
  - for long-term drainage of malignant effusions use: 1. Tunneled pleural catheter; 2. Pleural drainage and chemical pleurodesis
  - via facilitation of pleurodesis (obliteration of the pleural space by instilling talc or betadine to cause fibrosis and adherence of parietal and visceral pleura)

## Complications

- overall complications are rare (1-3%)
- malposition (most common complication), especially by inexperienced operators
  - tubes may dissect along the external chest wall, or may be placed below the diaphragm
- bleeding (anticoagulation is a relative contraindication)
- local infection, empyema
- perforation of lung parenchyma or vasculature
- risk of re-expansion pulmonary edema when large volumes of air or fluid are drawn off quickly (>1.0-1.5 L)

Tube thoracostomy can be completed under U/S guidance by an interventional radiologist or surgeon

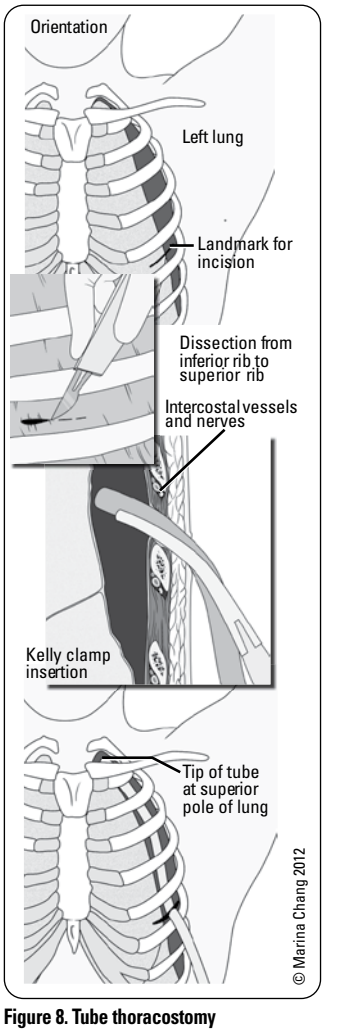



**Figure 8. Tube thoracostomy**

# Lung Cancer

## Classification

- lung tumours can be classified as primary or secondary, benign or malignant, endobronchial or parenchymal
- bronchogenic carcinoma (epithelial lung tumours) are the most common type of primary lung tumour (other types make up less than 1%)
  - small cell lung cancer (SCLC): 10-15%
  - non-small-cell lung cancer (NSCLC): 85-90%
    - squamous cell carcinoma: arise from the proximal respiratory epithelium
    - adenocarcinoma: incidence is increasing; most common subtype in nonsmokers
      - mucinous adenocarcinoma: grows along the alveolar wall in the periphery; may arise at sites of previous lung scarring
    - large cell undifferentiated cancer: diagnosis of exclusion
- benign epithelial lung tumours can be classified as papillomas or adenomas

**Table 5. Characteristics of Bronchogenic Cancer**

| Cell Type | Percentage of Bronchogenic Ca | Correlation with Smoking | Location | Histology | Metastasis | 5 Yr Survival Rates |
|---|---|---|---|---|---|---|
| **SCLC** | 10-15% | Strong | Central | Oat cell, neuroendocrine | Disseminated at presentation<br>Origin in endobronchial cells | 1% (poorest prognosis) |
| **Adenocarcinoma** | M: 35%<br>**F: 40%** | Weak | Peripheral | Glandular, mucin producing | Early, distant | 12% (60% for mucinous adenocarcinoma, a subtype, with a resectable solitary lesion) |
| **Squamous Cell Carcinoma (SCC)** | 30% | Strong | Central | Keratin, intercellular bridges | Local invasion and distant spread, may cavitate | 25% |
| **Large Cell Carcinoma** | 10-15% | Strong | Peripheral | Anaplastic, undifferentiated | Early, distant | 13% |

## Risk Factors

- cigarette smoking: the relative risk of developing lung cancer is 10-30 times higher for smokers than for nonsmokers
- risk of lung cancer increases with number of cigarettes smoked per day (linear) and duration of smoking (exponential)
- other risk factors include cigar smoking, pipe smoking, second-hand smoke, asbestos without smoking (relative risk is 5), asbestos with smoking (relative risk is 92), metals (e.g. chromium, arsenic, nickel), radon gas, ionizing radiation, and genetics

**Canadian Task Force on Preventative Health (2016)**
Screening with low-dose CT recommended for high-risk patients only:
- 55-74 years of age
- ≥30 pack yr smoking Hx
- AND, are a current smoker or quit within last 15 yr

Annual screening low-dose CT up to 3 years ONLY in centres with expertise in diagnosis and treatment of lung cancer

## Signs and Symptoms

- may be due to primary lesion, metastasis, or paraneoplastic syndrome
- primary lesion
  - cough (75%): beware of chronic cough that changes in character
  - dyspnea (60%)
  - chest pain (45%)
  - hemoptysis (35%)
  - other pain (25%)
  - clubbing (21%)
  - constitutional symptoms: anorexia, weight loss, fever, and fatigue
- metastasis
  - lung, hilum, mediastinum, pleura: pleural effusion, atelectasis, wheezing, postobstructive pneumonia
  - pericardium: pericardial effusion, pericardial tamponade
  - esophageal compression: dysphagia
  - phrenic nerve: paralyzed diaphragm
  - recurrent laryngeal nerve: hoarseness
  - superior vena cava syndrome
    - obstruction of SVC causing neck and facial swelling, as well as dyspnea and cough
    - other symptoms: hoarseness, tongue swelling, epistaxis, and hemoptysis
    - physical findings: dilated neck veins, increased number of collateral veins covering the anterior chest wall, cyanosis, edema of the face, arms, and chest, Pemberton's sign (facial flushing, cyanosis, and distension of neck veins upon raising both arms above head)
    - milder symptoms if obstruction is above the azygos vein
  - lung apex (Pancoast tumour): Horner's syndrome, brachial plexus palsy (most commonly C8 and T1 nerve roots)
  - rib and vertebrae: erosion
  - distant metastasis to brain, bone, liver, and adrenals
- paraneoplastic syndromes
  - a group of disorders associated with malignant disease, not related to the physical effects of the tumour itself
  - most often associated with SCLC

Malignant lung tumours are the most common cause of cancer mortality throughout the world in both men and women

**Horner has a MAP of the Coast**
A Pancoast tumour compresses the cervical sympathetic plexus causing a Horner's syndrome:
**M**iosis
**A**nhydrosis
**P**tosis

**Endobronchial Ultrasound (EBUS)**
- Allows visualization of peri-bronchial structures and distal peripheral lung lesions
- Provides detailed assessment of the airway wall layers
- Allows for guided biopsies of lymph nodes and tumours
- Used for diagnosis and staging

**Table 6. Paraneoplastic Syndromes**

| System | Clinical Feature | Associated Malignancy |
|---|---|---|
| **Skeletal** | Clubbing, hypertrophic pulmonary osteoarthropathy (HPOA) | Non-small cell lung cancer (NSCLC) |
| **Dermatologic** | Acanthosis nigricans<br>Dermatomyositis | Bronchogenic cancer<br>Bronchogenic cancer |
| **Endocrine** | Hypercalcemia (osteolysis or PTHrP)<br>Hypophosphatemia<br>Hypoglycemia<br>Cushing's syndrome (ACTH)<br>Somatostatinoma syndrome<br>SIADH | Squamous cell cancer<br>Squamous cell cancer<br>Sarcoma<br>Small cell lung cancer (SCLC)<br>Bronchial carcinoid<br>SCLC |
| **Neuromyopathic** | Lambert-Eaton syndrome<br>Polymyositis<br>Subacute cerebellar degeneration<br>Spinocerebellar degeneration<br>Peripheral neuropathy | SCLC |
| **Vascular/Hematologic** | Nonbacterial endocarditis<br>Trousseau's syndrome (migratory thrombophlebitis)<br>DIC | Bronchogenic cancer<br>NSCLC |
| **Renal** | Nephrotic syndrome | |

2/3 of primary lung cancer is found in the upper lung; 2/3 of metastases occur in the lower lung (hematogenous spread secondary to increased blood flow to the base of the lung)

**Postoperative Radiotherapy for NSCLC**
Cochrane DB Syst Rev 2016;10:CD002142
**Objective**: Evaluate effects of postoperative radiotherapy on survival and recurrence in patients with completely resected NSCLC.
**Methods**: MEDLINE and CANCERLIT searches and trial registers for trials of surgery vs. surgery plus radiotherapy in patients with NSCLC.
**Results**: 14 trials, 2343 participants. Postoperative radiotherapy had a significant adverse effect on survival (HR 1.18, 95% CI 1.07-1.31). This was equivalent to an absolute detriment of 5% at two years, reducing survival from 58 to 55%. Postoperative radiotherapy increased risk of recurrence (HR 1.10, 95% CI 0.99-1.21).
**Conclusions**: Postoperative radiotherapy is detrimental to those with completely resected NSCLC and should not be used in the routine treatment.

## Investigations

- initial diagnosis
  - imaging: CXR, CT chest + upper abdomen, PET scan
  - cytology: sputum
  - biopsy: bronchoscopy, EBUS, CT-guided percutaneous needle biopsy, mediastinoscopy
- staging workup
  - TNM staging system: T – primary tumour (size); N – regional lymph nodes; M – distant metastasis
  - blood work: electrolytes, LFTs, calcium, ALP
  - imaging: CXR, CT thorax and upper abdomen, bone scan, neuroimaging, PET scan
  - invasive: bronchoscopy (EBUS), mediastinoscopy, mediastinotomy, thoracotomy
  - screen adenocarcinoma for EGFR and ALK mutations

**Table 7. SCLC vs. NSCLC**

| | Stage | Definition | Treatment | Median Survival |
|---|---|---|---|---|
| **SCLC** | Limited stage | Confined to single radiation port (one hemithorax and regional lymph nodes) | Radiation ± chemotherapy ± prophylactic to brain | 1-2 yr (12 wk without treatment) |
| | Extensive stage | Extension beyond a single radiation port | Chemotherapy | 6 mo (5 wk without treatment) |
| | **Stage** | **TNM** | **Treatment** | **5 Yr Survival (%)*** |
| **NSCLC** | 0 | TisN0M0 | 1st line is complete surgical resection (VATS or open thoracotomy) with possible post-operative adjuvant chemotherapy with stage IB and stage II; radiotherapy for non-surgical candidates | 50 -73 |
| | IA | T1a-1bN0M0 | | 43-58 |
| | IB | T2aN0M0 | | 36-46 |
| | IIA | T1a-T2a,N1M0 or T2bN0M0 | | |
| | IIB | T2bN1M0 or T3N0M0 | | 25-36 |
| | IIIA | T1a-T2bN2M0 or T3N1-2M0 or T4N0-1M0 | Combined modality approach (chemotherapy, radiation therapy and sometimes surgical resection) | 19-24 |
| | IIIB | T4N2M0 or T1-4N3M0 | | 7-9 |
| | IV | T1-4N0-3M1a-1b | Systemic therapy or molecularly targeted therapy or symptom-based palliative management (radiation); isolated metastasis may be resected | 2-13 |

* Depends on clinical vs. pathologic stage  Refer to AJCC Cancer Staging Manual, 7th ed. 2010 for complete TNM classification

### Treatment

- options include surgery, radiotherapy, chemotherapy, and palliative care for end-stage disease
- surgery not usually performed for SCLC since it is generally non-curable
- contraindications for surgery
  - spread to contralateral lymph nodes or distant sites
    - patients with potentially resectable disease must undergo mediastinal node sampling since CT thorax is not accurate in 20-40% of cases
  - poor pulmonary status (e.g. unable to tolerate resection of lung)
    - post-op estimated $FEV_1$ and DLCO must be at least 40% of predicted to tolerate surgery
- chemotherapy (used in combination with other treatments)
  - common agents: etoposide, platinum agents (e.g. cisplatinum), ifosfamide, vincristine, anthracyclines, paclitaxel, irinotecan, gefitinib (an endothelial growth factor receptor inhibitor)
  - complications
    - acute: tumour lysis syndrome, infection, bleeding, myelosuppression, hemorrhagic cystitis (cyclophosphamide), cardiotoxicity (doxorubicin), renal toxicity (cisplatin), peripheral neuropathy (vincristine)
    - chronic: neurologic damage, leukemia, additional primary neoplasms

**Prevention**
Smoking cessation
Avoidance of exposures
Early detection

**Terminology**
- "nodule" <3 cm
- "mass" >3 cm

**Hamartomas**
- 10% of benign lung lesions
- Composed of tissues normally present in lung (fat, epithelium, fibrous tissue, and cartilage), but they exhibit disorganized growth
- Peak incidence is age 60, more common in men
- Usually peripheral and clinically silent
- CXR shows clustered "popcorn" pattern of calcification (pathognomonic for hamartoma)

Adenocarcinoma present in a non-smoker may be due to endothelial growth factor receptor mutation

**Corona Radiata Sign on Chest CT**
- Fine striations that extend linearly from a nodule in a spiculated fashion
- Highly associated with malignancy

**Carcinoids**
- Early onset (40-60 yr)
- Most are central and can produce symptoms and signs of bronchial obstruction
- Hemoptysis is present in ~50% of cases

# Approach to the Solitary Pulmonary Nodule

- see Medical Imaging, MI7

### Definition

- a round or oval, sharply circumscribed radiographic lesion up to 3 cm, which may or may not be calcified, and is surrounded by normal lung
- can be benign or malignant

Pulmonary neoplasms may present as a solitary pulmonary nodule identified incidentally on a radiographic study (~10% of cases) or as symptomatic disease (most cases)

**Table 8. Differential Diagnosis for Benign vs. Malignant Solitary Nodule**

| Benign (70%) | Malignant (30%) | |
|---|---|---|
| **Infectious granuloma** (histoplasmosis, coccidiomycosis, TB, atypical mycobacteria) - most common<br>**Other infections** (bacterial abscess, PCP, aspergilloma)<br>**Benign neoplasms** (hamartoma, lipoma, fibroma)<br>**Vascular** (AV malformation, pulmonary varix)<br>**Developmental** (bronchogenic cyst)<br>**Inflammatory** (granulomatosis with polyangiitis, rheumatoid nodule, sarcoidosis, amyloidosis)<br>**Other** (infarct, pseudotumour, rounded atelectasis, lymph nodes, amyloidoma) | **Bronchogenic carcinoma**<br>Adenocarcinoma<br>Squamous cell carcinoma<br>Large cell carcinoma<br>Small cell carcinoma | **Metastatic lesions**<br>Breast<br>Head and neck<br>Melanoma<br>Colon<br>Kidney<br>Sarcoma<br>Germ cell tumours<br>Pulmonary carcinoid |

### Investigations
- CXR: always compare with previous CXR
- CT densitometry and contrast enhanced CT of thorax
- sputum cytology: usually poor yield
- biopsy (bronchoscopic or percutaneous) or excision (thoracoscopy or thoracotomy): if clinical and radiographic features do not help distinguish between benign or malignant lesion
  - if at risk for lung cancer, biopsy may be performed regardless of radiographic features
  - if a biopsy is non-diagnostic, whether to observe, re-biopsy, or resect will depend on the level of suspicion
- watchful waiting: repeat CXR and/or CT scan at 3, 6, 12 mo
- PET scan can help distinguish benign from malignant nodules

**Table 9. CT Characteristics of Benign vs. Malignant Solitary Nodule**

| Parameters | Benign | Malignant |
|---|---|---|
| **Size** | Nodule (<3 cm) | Mass (>3 cm) |
| **Borders** | Smooth or lobulated | Irregular or spiculated |
| **Features** | Calcified pattern: diffuse, central, laminated, "popcorn" pattern if hamartoma, usually no cavitation; if cavitating, wall is smooth and thin, no other lung pathology | Usually not calcified; if calcified, pattern is eccentric, stippled, no satellite lesions, cavitation with thick wall, may have pleural effusions, lymphadenopathy |
| **Doubling Time** | Doubles in <20 or >400 d | Doubles between 20 and 400 d |

**Table 10. Evaluation of a Solitary Pulmonary Nodule**

| SOLID NODULES | | | |
|---|---|---|---|
| **Nodule Type** | **Size <6 mm (<100 mm²)** | **Size 6-8 mm (100-250 mm²)** | **Size >8 mm (>250 mm²)** |
| **Single** | | | |
| **Low Risk** | No routine follow-up | CT at 6-12 mo, then consider CT at 18-24 mo | Consider CT a 3 mo, PET/CT or tissue sampling |
| **High Risk** | Optional CT at 12 mo | CT at 6-12 mo then at 18-24 mo | Consider CT a 3 mo, PET/CT or tissue sampling |
| **Multiple** | | | |
| **Low Risk** | No routine follow-up | CT at 3-6 mo, then consider CT at 18-24 mo | CT at 3-6 mo, then consider CT at 18-24 mo |
| **High Risk** | Optional CT at 12 mo | CT at 3-6 mo then at 18-24 mo | CT at 3-6 mo then at 18-24 mo |

| SUBSOLID NODULES | | |
|---|---|---|
| **Nodule Type** | **Size <6 mm (<100 mm²)** | **Size ≥6 mm (>100 mm²)** |
| **Single** | | |
| **Ground Glass** | No routine follow-up | CT at 6-12 mo to confirm persistence then CT every 2 yr until 5 yr |
| **Part Solid** | No routine follow-up | CT at 3-6 mo to confirm persistence<br>If unchanged and solid component remains <6 mm, annual CT should be performed for 5 yr |
| **Multiple** | CT at 3-6 mo. If stable consider CT at 2 and 4 yr | CT at 3-6 mo.<br>Subsequent management based on the most suspicious nodule(s) |

Adapted from: MacMahon H, Naidich DP, Goo JM, et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images. The Fleischner Society 2017. Radiology Journal. doi:10.1148/radiol.2017161659. Feb 23 2017.

# Lung Transplantation

### Conditions Leading to Transplantation
- chronic acquired lung disease: COPD
- genetic: CF, and emphysema due to α-1 antitrypsin deficiency
- idiopathic interstitial pneumonias: IPF, and nonspecific interstitial pneumonitis
- HTN-related: idiopathic pulmonary arterial HTN (IPAH), secondary pulmonary HTN, and Eisenmenger's syndrome
- other: sarcoidosis, lymphangioleiomyomatosis, and pulmonary Langerhans cell histiocytosis

### Clinical Indications
- transplantation should be considered for patients with advanced lung disease refractory to maximal medical or surgical therapy
- patients who are symptomatic during activities of daily living and have risk of death >50% over the next 2 yr

### Criteria for Transplantation
- lung allocation score based on: 1) post-transplant survival measure, and 2) waiting list urgency measure
- transplant benefit = post-transplant survival (days) – waitlist survival (days)

### Contraindications
- unstable medical condition such as acute sepsis or poorly controlled dysfunction of another organ system (e.g. heart, liver, kidney or brain)
- malignancy in the last 2 yr
- uncorrected CAD with end organ ischemia or CAD not amenable to revascularization
- significant chest wall/spinal deformity
- active cigarette smoking, and BMI ≥35
- HIV infection, ongoing HBV, HCV, or TB infections
- inadequate social supports, functional limitation to participate in rehab, psychological issues reducing compliance with medical regimen

### Post-Operative Complications
- primary graft dysfunction (main cause is ischemia-reperfusion injury)
- airway anastomotic complications (focal infection, bronchial necrosis and dehiscence, excess granulation tissue, tracheobronchomalacia, stenosis, and fistula)
- chronic graft dysfunction (bronchiolitis obliterans syndrome, and restrictive allograft syndrome)
- infectious complications (bacterial, fungal, CMV, community-acquired respiratory viruses, and mycobacteria)
- malignancy (non-melanoma skin cancer, post-transplant lymphoproliferative disease, colon, breast, Kaposi's sarcoma, and bladder)

### Prognosis
- median survival for all adult recipients: 5.7 yr
- 1 yr survival: COPD > IPF > IPAH
- 10 yr survival: CF, α-1 antitrypsin deficiency > IPAH > COPD, IPF

## Chronic Obstructive Pulmonary Disease

- see Respirology, R9

### Treatment
- indications for surgical management
  - dyspnea despite maximal medical therapy and pulmonary rehabilitation
  - CT showing hyperinflation and heterogeneously distributed emphysema predominant in the upper lung zone
  - may be used as a bridging procedure to lung transplantation
- contraindications
  - age >75, cigarette smoking within the prior 6 mo, higher risk of surgical mortality
  - homogeneously distributed emphysematous changes without areas of preserved lung tissue
  - diffusing capacity of lung for carbon monoxide <20% of predicted, $PaCO_2$ >60 mmHg, $PaO_2$ <45 mmHg
- surgical procedures
  - lung volume reduction surgery: wedge excision of emphysematous tissue
  - bilateral or unilateral, thoracotomy or VATS



**Long-Term Survival Analysis of the Canadian Lung Volume Reduction Surgery Trial**
Ann Thorac Surg 2013;96:1217-1222
**Study**: Retrospective observational study assessing the long-term survival of patients enrolled in the CLVRS at 8-10 yr follow-up.
**Results/Conclusions**: Compared with the best medical care group, patients in the LVRS group showed a 16-mo survival advantage and a 20% reduction in mortality. Although not statistically significant, LVRS may provide long-term benefits in the treatment of end-stage emphysema.

### Complications of Treatment
- air leak: may require reintubation and mechanical ventilation
- arrhythmias, pneumonia

### Prognosis
- worse early mortality but better exercise capacity and quality of life with LVRS

# Stomach and Duodenum

## Peptic Ulcer Disease

### GASTRIC ULCERS

- see Gastroenterology, G11

#### Indications for Surgery

- refractory to medical management
- suspicion of malignancy (even if biopsy benign)
- complications of PUD: obstruction, perforation, and bleeding (3x greater risk compared to duodenal ulcers)
- surgery increasingly rare due to H. pylori eradication, medical treatment and endoscopic treatments (injection therapy with adrenaline, polidocanol or fibrin glue) or coagulation therapy (heater probe or argon plasma)

#### Procedures

- ligation of bleeding vessels
- distal gastrectomy with ulcer excision: Billroth II, Roux-en-Y gastrojejunostomy or Billroth I (rarely) reconstruction
- vagotomy and pyloroplasty only if acid hypersecretion (very rare)
- wedge resection if possible
- biopsy for suspicion of malignancy, followed by gastroscopy to minimize further bleeding and aid with healing

### DUODENAL ULCERS

- see Gastroenterology, *Bleeding Peptic Ulcer*, G12, and *Peptic Ulcer Disease*, G11
- most within 2 cm of pylorus (duodenal bulb)

#### Indications for Surgery

- hemorrhage, rebleed in hospital, perforation, gastric outlet obstruction
- refractory to medical and endoscopic management

#### Procedures

- omental (Graham) patch: plication of ulcer supported by overlying omental patch
- oversewing of bleeding ulcer ± pyloroplasty
- treat with *H.plyori* eradication protocol post operatively

#### Complications of Gastric Surgery

- retained antrum
- fistula (gastrocolic/gastrojejunal)
- dumping syndrome, postvagotomy diarrhea, afferent loop syndrome

**Table 11. Complications of Duodenal Ulceration**

| Complication | Clinical Features | Management |
|---|---|---|
| **Perforated Ulcer** (typically on anterior surface) | Sudden onset of pain (possibly in RLQ due to track down right paracolic gutter)<br>Acute abdomen: rigid, diffuse guarding<br>Ileus<br>Initial chemical peritonitis followed by bacterial peritonitis | Investigation<br>CXR – free air under diaphragm (70% of patients)<br><br>Treatment<br>Oversew ulcer (plication) and omental (Graham) patch – most common treatment |
| **Penetration to Nearby Organs** | Elevated amylase/lipase if penetration into pancreas<br>Elevated hepatic transaminases if penetration into liver (rare, but serious)<br>Constant mid-epigastric pain burrowing into back, unrelated to meals | |
| **Hemorrhage** (typically on posterior surface) | Gastroduodenal artery involvement | Resuscitation initially with crystalloids; blood transfusion if necessary<br>Diagnostic and/or therapeutic endoscopy (laser, cautery, or injection); if recurs, may have second scope<br>Consider interventional radiology: angiography with embolization/coiling<br>Surgery if severe or recurrent bleeding, hemodynamically unstable, or failure of endoscopy and IR: oversewing of ulcer, pyloroplasty |
| **Gastric Outlet Obstruction** | Ulcer can lead to edema, fibrosis of pyloric channel, and neoplasm<br>N/V (undigested food, non-bilious), dilated stomach, and crampy abdominal pain<br>Succussion splash (splashing noise heard with stethoscope over the stomach when patient is shaken)<br>Auscultate gas and fluid movement in obstructed organ | NGT decompression and correction of hypochloremic, hypokalemic metabolic alkalosis<br>Medical management initially: high dose PPI therapy<br>Surgical resection if obstruction does not resolve: either Billroth I, pyloroplasty, or gastrojejunostomy |

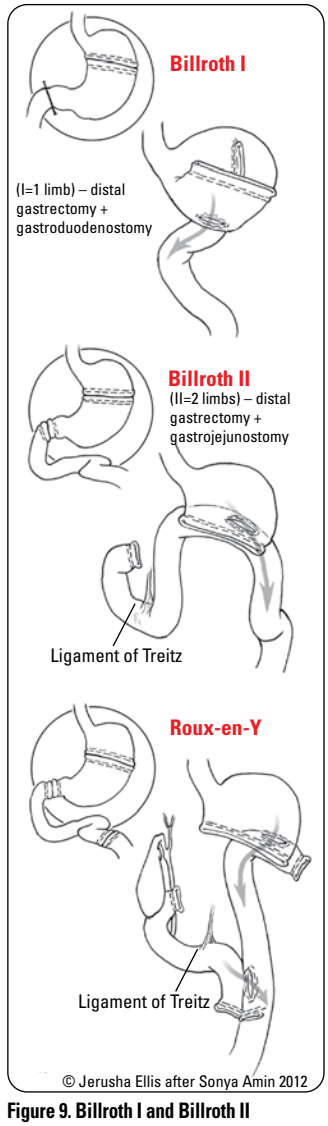



**Figure 9. Billroth I and Billroth II with Roux-en-Y reconstruction (gastrojejunostomy)**

**Kissing Ulcer**: combination of perforation and bleeding

# Gastric Carcinoma

## Epidemiology
- 5th most common cancer in the world
- M:F = 3:2
- most common age group = 50-59 yr
- incidence has decreased by 2/3 in past 50 yr
- incidence of adenocarcinoma <10 (US) vs. 40 (Japan, Korea) per 100,000 (incidence highest in Asia, Latin America, and Caribbean)

**Signs of Metastatic Gastric Carcinoma**
**Virchow's node**: left supraclavicular node
**Blumer's shelf**: mass in pouch of Douglas
**Krukenberg tumour**: metastases to ovary
**Sister Mary Joseph node**: umbilical metastases
**Irish's node**: left axillary nodes

## Risk Factors
- compensatory epithelial cell proliferation via gastric atrophy from:
  - *H. pylori*, causing chronic atrophic gastritis
  - pernicious anemia associated with achlorhydria and chronic atrophic gastritis
  - previous partial gastrectomy (>10 yr post-gastrectomy)
- host-related factors
  - blood type A
  - hereditary nonpolyposis colorectal cancer (HNPCC), hereditary diffuse gastric carcinoma (HDGC)
  - gastric adenomatous polyps
  - hypertrophic gastropathy
  - genetic syndromes: hereditary diffuse gastric cancer E-cahedrin (CDH-1) gene
- patient and lifestyle factors: high BMI, smoking, alcohol, smoked food, and nitrosamines

## Clinical Features
- clinical suspicion
  - ulcer fails to heal
  - lesion on greater curvature of stomach or cardia
- asymptomatic, insidious, or late onset of symptoms
  - postprandial abdominal fullness, pseudoachalasia (in older patients), vague epigastric pain
  - anorexia or weight loss
  - burping, N/V, dyspepsia, and dysphagia
  - hepatomegaly, epigastric mass (25%)
  - hematemesis, fecal occult blood, melena, and iron-deficiency anemia
- metastasis
  - peritoneum, ovarian, liver, lung, and brain

**Staging and 5 Yr Survival Rates for Gastric Cancer**

| Stage | TNM | 5-Yr Survival |
|---|---|---|
| IA | T1N0M0 | 71% |
| IB | T2N0M0 | 57% |
| | T1N1M0 | |
| IIA | T3N0M0 | 45% |
| | T2N1M0 | |
| | T1T2M0 | |
| IIB | T4aN0M0 | 33% |
| | T3N1M0 | |
| | T2N2M0 | |
| | T1N3M0 | |
| IIIA | T4aN1M0 | 20% |
| | T3T2M0 | |
| | T2N3M0 | |
| IIIB | T4bN0M0 | 14% |
| | T4bN1M0 | |
| | T4aN2M0 | |
| | T3N3M0 | |
| IIIC | T4bN2M0 | 9% |
| | T4bN3M0 | |
| | T4aN3M0 | |
| IV | TxNxM1 | 4% |

## Investigations
- OGD and biopsy; consider EUS to assess pre-operative T-stage and N-stage
- CT chest/abdomen/pelvis (for Metastatic Workup see Table 14)

**Table 12. TNM Classification System for Staging of Gastric Carcinoma (AJCC/IUCC 2017, 8th edition)**

| Primary Tumour (T) | | Regional Lymph Nodes (N) | | Distant Metastasis (M) | |
|---|---|---|---|---|---|
| TX | Primary tumour cannot be assessed | NX | Cannot be assessed | M0 | No distant metastasis |
| T0 | No evidence of primary tumour | N0 | No regional node metastasis | M1 | Distant metastasis |
| Tis | *Carcinoma in situ* | N1 | Metastasis in 1-2 regional nodes | | |
| T1a | Invasion into lamina propria or muscularis mucosae | N2 | Metastasis in 3-6 regional nodes | | |
| T1b | Invasion into submucosa | N3a | Metastasis in 7-15 regional nodes | | |
| T2 | Invasion into muscularis propria | N3b | Metastasis in ≥16 regional nodes | | |
| T3 | Penetration of subserosal connective tissue without tissue invasion of visceral peritoneum or adjacent structures | | | | |
| T4a | Invasion into serosa | | | | |
| T4b | Invasion into adjacent structures | | | | |

## Treatment
- adenocarcinoma
  - proximal lesions
    - total gastrectomy and Roux-en-Y esophagojejunostomy
  - distal lesions
    - subtotal gastrectomy: wide margins, en bloc removal of omentum and lymph nodes with Roux-en-Y or Billroth II reconstruction
  - adjuvant therapies
    - perioperative chemotherapy or post-operative chemoradiotherapy in addition to surgery is standard of care in curative intent strategy
  - palliation
    - limited gastric resection or endoscopic stenting to decrease bleeding and relieve obstruction, enables the patient to eat
    - radiation therapy
    - studies are showing larger role for adjuvant/neoadjuvant and palliative chemotherapy
- lymphoma
  - *H. pylori* eradication, chemotherapy ± radiation, and surgery in limited cases (perforation, bleeding, and obstruction)

# Gastrointestinal Stromal Tumour

## Epidemiology
- most common mesenchymal neoplasm of GI tract
- derived from interstitial cells of Cajal (cells associated with Auerbach's plexus that have autonomous pacemaker function which coordinate peristalsis throughout the GI tract)
- 75-80% associated with tyrosine kinase (c-KIT) mutations
- most common in stomach (50%) and proximal small intestine (25%), but can occur anywhere along GI tract
- typically present with vague abdominal mass, feeling of abdominal fullness, or with secondary symptoms of bleeding and anemia
- often discovered incidentally on CT, laparotomy, or endoscopy

## Risk Factors
- Carney's triad: GISTs, paraganglioma, and pulmonary chondroma
- Type I neurofibromatosis

## Investigations
- pre-operative biopsy (endoscopic ultrasound): useful for indeterminate lesions (not recommended if high index of suspicion for GIST)
- contrast-enhanced CT is preferred Imaging for screening and staging; MRI if IV contrast not feasible

## Treatment
- surgical resection if >2 cm; follow with serial endoscopy if <2 cm and resect if growing or symptomatic
- localized GIST
  - surgical resection with preservation of intact pseudocapsule
  - lymphadenectomy NOT required, as GISTs rarely metastasize to lymph nodes
  - consider adjuvant treatment with imatinib (Gleevec) if high risk of relapse (large, >4 cm with significant mitotic activity)
- advanced disease (i.e. metastases to liver and/or peritoneal cavity)
  - palliative intent chemotherapy with imatinib
  - metastectomy may be considered for liver limited disease

## Prognosis
- risk of metastatic potential depends on
  - tumour size (worse if >10 cm)
  - mitotic activity (worse if >5 mitotic figures or 50/hpf)
  - degree of nuclear pleomorphism
  - location: with identical sizes, extra-gastric location has a higher risk of progression than GISTs in the stomach
- metastases to liver, omentum, peritoneum; nodal metastases rare

**Neoadjuvant Chemotherapy in Advanced Gastric and Esophago-Gastric Cancer. Meta-Analysis of Randomized Trials**
Int J Surg 2018;51:120-127
**Study**: Meta-analysis evaluating the effects of neoadjuvant chemotherapy on advanced gastric cancer.
**Results**: Neoadjuvant chemotherapy and resection reduces overall mortality at 3 and 5-years in advanced gastric cancer (RR = 0.74; 0.82 respectively). Morbidity and perioperative mortality rate are not influenced by NACT. Recurrence rate is reduced by NACT + surgery in EGC (RR = 0.80).

**Extent of Lymph Node Dissection for Adenocarcinoma of the Stomach**
Cochrane DB Syst Rev 2015;12:CD001964
**Study**: Systematic review and meta-analysis on the evidence that existed regarding the impact of the three main types of progressively more extended lymph node dissection (that is, D1, D2 and D3 lymphadenectomy) on the clinical outcome of patients with primary resectable carcinoma of the stomach.
**Results/Conclusions**: Data suggested no significant difference in overall survival between D2 and D3 type dissection. There was no significant difference in overall survival between D1 and D2 type node dissection. In contrast, D2 lymphadenectomy was associated with a significantly better disease specific survival compared to D1 lymphadenectomy but was also associated with a higher postoperative mortality rate.

# Bariatric Surgery

- weight reduction surgery for morbid obesity
- indications: BMI ≥40 without illness or BMI ≥35 with 1+ serious comorbidity (e.g. DM, CAD, sleep apnea, GERD, or severe joint disease)

## Surgical Options
- combination malabsorptive and restrictive
  - laparoscopic Roux-en-Y gastric bypass (most common, most effective; higher complication rates)
    - small gastric pouch (restrictive), from distal stomach, anastomosed with Roux limb of small bowel (malabsorptive); connect to biliopancreatic limb to maintain digestive enzymes and bile
  - restrictive laparoscopic sleeve gastrectomy (only consider for severe obesity)
    - creation of tubular stomach via removal of majority of greater curvature
  - laparoscopic adjustable gastric banding (modest expected weight loss, declining in popularity)
    - inflatable silicone band around fundus, adjustable via subcutaneous port
- malabsorptive
  - biliopancreatic diversion with duodenal switch
    - anastomosis of stomach to distal ileum, anastamosis of biliopancreatic limb to terminal Ileum

## Complications
- perioperative mortality ~1% (anastomotic leak with peritoneal signs, PE)
- obstruction at enteroenterostomy (see *Complications of Gastric Surgery*, GS18)
- staple line dehiscence
- dumping syndrome
- cholelithiasis due to rapid weight loss (20-30%)
- band abscess (if long-term)

**Surgery for Weight Loss in Adults**
Cochrane DB Syst Rev 2014;8:CD003641
**Study**: This is an update of a Cochrane review first published in 2003 assessing the effects of bariatric surgery and control of comorbidities.
**Conclusions**: Surgery resulted in decreased BMI one to two years post-op. 3 RCTs found that laparoscopic Roux-en-Y gastric bypass achieved significantly greater weight loss and body mass index (BMI) reduction up to five years after surgery compared with laparoscopic adjustable gastric banding (mean difference -5.2 kg/m$^2$; 95% CI -6.4 to -4.0). More patients experienced remission of diabetes, however, different definitions used. Risks of surgery include leaks, hernias, infection, pulmonary embolism, cholecystitis, and post-operative mortality.

# Complications of Gastric Surgery

- most resolve within 1 yr

### Alkaline Reflux Gastritis
- duodenal contents (bilious) reflux into stomach causing gastritis ± esophagitis
- treatment
  - medical: H2-blocker, metoclopramide, cholestyramine (bile acid sequestrant)
  - surgical: conversion of Billroth I or II to Roux-en-Y

### Afferent Loop Syndrome
- accumulation of bile and pancreatic secretions causes intermittent mechanical obstruction and distention of afferent limb
- clinical features
  - early postprandial distention, RUQ pain, nausea, bilious vomiting, anemia
- treatment: surgery (conversion to Roux-en-Y increases afferent loop drainage)

### Dumping Syndrome
- early: 15-30 min post-prandial
  - etiology
    - rapid emptying of hyperosmotic chyme leads to jejunal distention, stimulating release of vasoactive hormones
  - clinical features
    - post-prandial epigastric cramping, bloating, emesis, nausea, and vasomotor symptoms (dizziness, palpitations, tachycardia, diaphoresis)
  - treatment
    - frequent small meals high in fibre and protein, low in carbohydrates; avoidance of liquids with meals
    - last resort is interposition of antiperistaltic jejunal loop between stomach and small bowel to delay gastric emptying
- late: 3 h post-prandial
  - etiology: hypoglycemia following postprandial insulin peak
  - treatment: small snack 2 h after meals

### Blind-Loop Syndrome
- bacterial overgrowth of colonic Gram-negative bacteria in afferent limb
- clinical features
  - anemia/weakness, diarrhea, malnutrition, abdominal pain, and hypocalcemia
- treatment: broad-spectrum antibiotics, and surgery (conversion to Billroth I)

### Postvagotomy Diarrhea
- up to 25%
- bile salts in colon inhibit water resorption
- treatment: medical (cholestyramine), and surgical (reversed interposition jejunal segment)

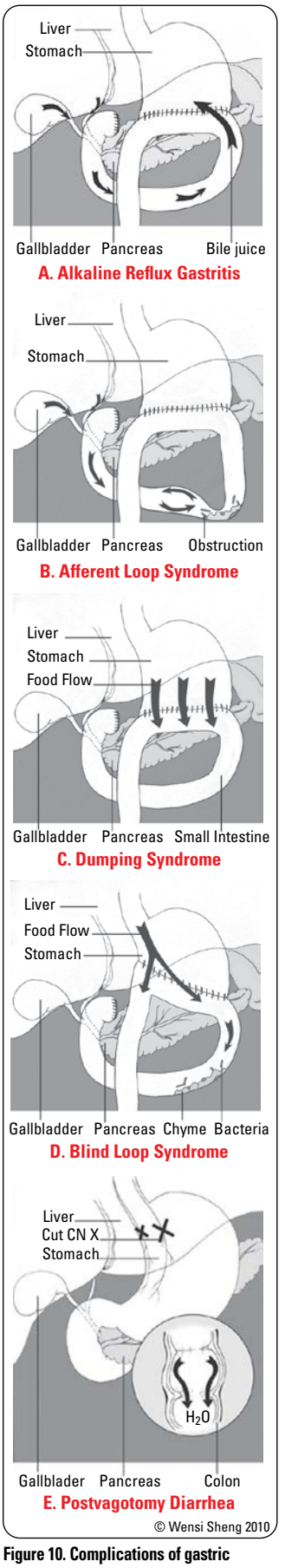



**Figure 10. Complications of gastric surgery**

# SMALL INTESTINE

# Small Bowel Obstruction

## Mechanical Small Bowel Obstruction

### Pathophysiology
- obstruction → gas and fluid (swallowed or GI secretions) accumulate proximal to site of obstruction and distal decompression → intestinal activity increases to overcome obstruction → colicky pain and diarrhea (initially)
- bowel wall edema and disruption of normal bowel absorptive function can lead to increased intraluminal fluid, transudative fluid loss into peritoneal cavity, and electrolyte disturbances, which is worsened by vomiting
- increase intramural pressure can lead to impaired microvascular perfusion leading to intestinal ischemia and necrosis (strangulated bowel obstruction)

### Etiology

**Table 13. Common Causes of SBO**

| Intraluminal | Intramural | Extramural |
|---|---|---|
| Intussusception | Crohn's | Adhesions from previous surgeries (75% SBO) |
| Gallstones | Radiation stricture | Incarcerated hernia |
| Bezoars | Adenocarcinoma | Peritoneal carcinomatosis |

- three types
  - partial SBO: only a portion of intestinal lumen is occluded, allows passage of some gas & fluid, low risk of strangulation
  - complete SBO: the lumen of the intestine is occluded, no passage of gas or stool, at higher risk of strangulation
  - closed-loop obstruction: segment of intestine is obstructed both proximally and distally (e.g. volvulus), leading to rapid rise in intraluminal pressure from gas and fluid that cannot escape, high risk of strangulation due to bowel wall ischemia

## Risk Factors
- prior abdominal or pelvic surgery
- abdominal wall or groin hernia
- history of malignancy
- prior radiation

## Clinical Features
- 1) distinguish mechanical obstruction from ileus; 2) determine likely and easily reversible etiology of obstruction; 3) differentiate complicated (e.g. strangulated) obstruction
- symptoms: colicky abdominal pain, nausea/vomiting, obstipation
  - more feculent vomitus suggests more established obstruction because of bacterial overgrowth
  - passage of gas and/or stool that continues 6-12 h after onset of symptoms suggests partial rather than complete obstruction
- signs: abdominal distention (most prominent if obstruction at distal ileum), hyperactive proceeding to minimal bowel sound
- strangulated obstruction: abdominal pain disproportionate to physical exam findings suggest intestinal ischemia
  - may have tachycardia, localized abdominal tenderness, fever, marked leukocytosis, and lactate acidosis

## Investigations
- radiological
  - abdominal x-ray (3 views): triad of dilated small bowel (>3 cm in diameter), air-fluid levels on upright film, paucity of air in colon (high sensitivity, low specificity as ileus and LBO can present similarly)
  - CT: discrete transition zone/point with proximal bowel dilation, distal bowel decompression, and intraluminal contrast does not pass the transition zone
    - most importantly to rule out ischemic bowel/strangulation: pneumatosis intestinalis (free air in bowel wall) and thickened bowel wall, air in portal vein, free intraperitoneal fluids, and differential wall enhancements (poor uptake of IV contrast into the wall of the affected bowel)
  - other
    - less used: upper GI series/small bowel series (if no cause apparent, i.e. no hernias, and no previous surgeries) or serial CTs with oral contrast
    - may consider U/S or MRI in pregnant patients
- laboratory
  - may be normal early in disease course
  - creatinine, and hematocrit to assess degree of dehydration
  - fluid, and electrolyte abnormalities; metabolic alkalosis due to frequent emesis; amylase elevated
  - if strangulation: leukocytosis with left shift, elevated lactate (late signs)

## Treatment
- IV isotonic fluid resuscitation and urine output monitoring with catheter
  - SBO related vomiting and decrease PO intake leads to volume depletion
- NG tube in the stomach for gastric decompression; decrease nausea, distention, and risk of aspiration from vomiting
- NPO
- Partial SBO/Crohn's/Carcinomatosis: conservative management with fluid resuscitation and NG tube decompression
  - 48 h of watchful waiting; if no improvement or develops complications, surgery
  - For Crohn's patients, consider GI consult for steroid management
- if no clinical features of ischemia, short course of conservative management with fluid resuscitation and NG tube decompression with frequent re-examination by surgical team
  - duration of observation varies from hours to a few days
  - if SBO fails to resolve, or if symptoms of ischemia develop, then surgery

- high risk for ischemia based on clinical symptoms: urgent surgery to prevent irreversible ischemia
  - early post-operative SBO: if bowel function does not return within 3-5 d after surgery; usually partial, extended conservative therapy (2-3 wk) with bowel rest, fluids, and TPN is appropriate
- surgery if presence of ischemia or perforation demonstrated



**MUST DO**
Rule out CRC in constipated patient
Send for TURP in patient with BPH (treat intra-abdominal HTN)



**Increased Risk of Perforation with Distention as seen on Abdomen Imaging**
- Small bowel ≥3 cm
- Distal colon ≥6 cm
- Proximal colon ≥9 cm
- Cecum ≥12 cm



Important to know if chronic vs acute. Chronic distention is tolerated more likely without perforation



Patients presenting with a SBO in setting of "virgin" abdomen should have surgery ASAP – EXCEPTION: malignant obstruction from history and imaging



In a non-virgin abdomen – adhesional SBOs resolve spontaneously with NGT decompression 70% of time



**Top 3 Causes of SBO (in order)**

**ABC**
**A**dhesions
**B**ulge (hernias)
**C**ancer (neoplasms)



**Causes of SBO**

**SHAVING**
**S**tricture
**H**ernia
**A**dhesions
**V**olvulus
**I**ntussusception/**I**BD
**N**eoplasm
**G**allstones

### Prognosis
- related to etiology; mortality: non-strangulating <1%, strangulating 8% (25% if >36 h), ischemic = up to 50%

### Prevention
- open surgery has four fold increase in risk of SBO in 5 yr compared to laparoscopic surgery

## Paralytic Ileus

### Pathogenesis
- temporary, reversible impairment of intestinal motility; mostly frequently caused by:
  - abdominal operations, infections and inflammation, medications (opiates, anesthetics, psychotropics), and electrolyte abnormalities
  - passing gas is the most useful indicator
- NOT the same as intestinal pseudo-obstruction
  - chronic pseudo-obstruction refers to specific disorders that affect the smooth muscle and myenteric plexus, leading to irreversible intestinal dysmotility

### Clinical Features
- symptoms and signs of intestinal obstruction without mechanical obstruction
  - bowel sounds are diminished or absent (in contrast to initial hyperactive bowel sounds in SBO)
  - may have liquid stools as well

### Investigations
- routine post-operative ileus: expected, no investigation needed
- if ileus persists or occurs without abdominal surgery
  - review patient medications (especially opiates)
  - measure serum electrolyte to monitor for electrolyte abnormalities (including extended electrolytes like Mg, Ca, $PO_4$)
  - CT scan to rule out abscess or peritoneal sepsis, or to exclude mechanical obstruction

### Treatment
- most important: NPO + fluid resuscitation
- NGT decompression, correct causative abnormalities (e.g. sepsis, medications, and electrolytes), consider TPN for prolonged ileus
- post-operative: gastric and small bowel motility returns by 24-48 h, colonic motility by 3-5 d
- current interest in novel therapies such as gum chewing and pharmacologic therapy (e.g. alvimopan, an opioid antagonists)

## Intestinal Ischemia

### Etiology
- acute
  - arterio-occlusive mesenteric ischemia (AOMI)
    - thrombotic, embolic, and extrinsic compression (e.g. strangulating hernia)
  - non-occlusive mesenteric ischemia (NOMI)
    - mesenteric vasoconstriction secondary to systemic hypoperfusion (preserves supply to vital organs)
  - mesenteric venous thrombosis (MVT)
    - consider hypercoagulable state (i.e. rule out malignancy), and DVT (prevents venous outflow)
- chronic: usually due to atherosclerotic disease – look for CVD risk factors
- can lead to occlusion in vessels that supplies the small intestine and the large intestine

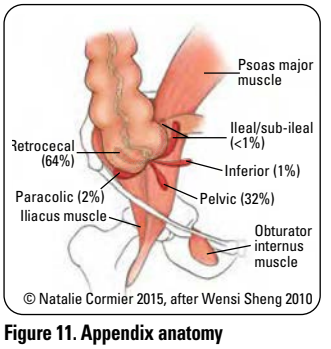



**Figure 11. Appendix anatomy**

### Clinical Features
- acute: severe abdominal pain out of proportion to physical findings, vomiting, bloody diarrhea, bloating, minimal peritoneal signs early in course, hypotension, shock, and sepsis
- chronic: postprandial pain (from mesenteric angina), fear of eating, and weight loss
- common sites: SMA supplied territory, "watershed" areas of colon – splenic flexure, left colon, and sigmoid colon

Pain "out of keeping with physical findings" is the hallmark of early intestinal ischemia

### Investigations
- laboratory: leukocytosis (non-specific), and lactic acidosis (late finding)
  - amylase, lactate, CK, and ALP can be used to observe progress
  - hypercoagulability workup if suspect venous thrombosis
- AXR: portal venous gas, intestinal pneumatosis, and free air if perforation
- contrast CT: thickened bowel wall, luminal dilatation, SMA or SMV thrombus, mesenteric/portal venous gas, and pneumatosis
- CT angiography is the gold standard for acute arterial ischemia

### Treatment

- fluid resuscitation, correct metabolic acidosis, NPO, NGT decompression of stomach, and prophylactic broad-spectrum antibiotics; avoid vasoconstrictors and digitalis
- exploratory laparotomy/laparoscopy to assess extent of viability ± segmental resection of necrotic intestine
  - if extent of bowel viability is uncertain, a second-look laparotomy 12-24 h later is mandatory
- angiogram, embolectomy/thrombectomy, bypass/graft, mesenteric endarterectomy, anticoagulation therapy, and percutaneous transluminal angioplasty ± stent



An acute abdomen + metabolic acidosis is bowel ischemia until proven otherwise

# Tumours of Small Intestine

## BENIGN TUMOURS

- 10x more common than malignant
- usually asymptomatic until large
- most common sites: terminal ileum and proximal jejunum
- polyps
  - adenomas
  - hamartomas
  - FAP (see *Familial Colon Cancer Syndromes*, GS38)
  - juvenile polyps
- other: leiomyomas, lipomas, and hemangiomas



**Carcinoid Syndrome Symptoms**

**FDR**
**F**lushing
**D**iarrhea
**R**ight-sided heart failure

**Table 14. Malignant Tumours of the Small Intestine**

| | Adenocarcinoma | Carcinoid/GI NET-Neuroendocrine Tumour | Lymphoma | Metastatic |
|---|---|---|---|---|
| **Epidemiology** | Usually 50-70 yr<br>M>F | Increased incidence 50-60 yr | Highest incidence in 70s<br>M>F<br>Usually non-Hodgkin's lymphoma | Most common site of GI metastases in patients with metastatic melanoma |
| **Risk Factors** | Crohn's, FAP, history of CRC, HNPCC | | Crohn's, celiac disease, autoimmune disease, immunosuppression, radiation therapy, and nodular lymphoid hyperplasia | Melanoma, breast, lung, ovary, colon, and cervical cancer |
| **Origin/Location** | Usually in proximal small bowel, incidence decreases distally | Classified based on embryological origin (foregut, midgut, and hindgut)<br>Originate from gut enterochromaffin cell<br>Appendix 46%, distal ileum 28%, rectum 17% | Usually distal ileum<br>Proximal jejunum in patients with celiac disease | Hematogenous spread from breast, lung, and kidney<br>Direct extension from cervix, ovaries, and colon |
| **Clinical Features** | Early metastasis to lymph nodes<br>80% metastatic at time of operation<br>Abdominal pain (common) | N/V, anemia, GI bleeding, jaundice, and weight loss (less common)<br>Often slow-growing<br>Usually asymptomatic, incidental finding<br>Obstruction, bleeding, crampy abdominal pain, and intussusception<br>Carcinoid syndrome (<10%)<br>Hot flashes, hypotension, diarrhea, bronchoconstriction, and right heart failure<br>Requires liver involvement: lesion secretes serotonin, kinins, and vasoactive peptides directly to systemic circulation (normally inactivated by liver) | Fatigue, weight loss, fever malabsorption, abdominal pain, anorexia, vomiting, constipation, and mass<br>Rarely – perforation, obstruction, bleeding, and intussusception | Obstruction and bleeding |
| **Investigations** | CT abdomen/pelvis<br>Endoscopy | Most found incidentally at surgery for obstruction or appendectomy<br>CT thorax/abdomen/pelvis<br>Consider small bowel enteroclysis to look for primary<br>Serum chromogranin A as a tumour marker<br>Elevated 5-HIAA (breakdown product of serotonin) in urine or increased 5-HT in blood<br>Radiolabelled octreotide or MIBG scans to search for metastases and locate tumour | CT abdomen/pelvis | CT abdomen/pelvis |
| **Treatment** | Surgical resection ± chemotherapy | Surgical resection ± chemotherapy<br>Carcinoid syndrome treated with steroids, histamine, and octreotide<br>Metastatic risk 2% if size <1 cm, 90% if >2 cm | Low grade: chemotherapy with cyclophosphamide<br>High grade: surgical resection, and radiation<br>Palliative: somatostatin, doxorubicin | Palliation |
| **Prognosis** | 5 yr survival 25% (if node positive) | 5 yr survival 70%; 20% with liver metastases<br>Based on the Ki67 index | 5 yr survival 40% | Poor |
| **Staging System** | TNM | TNM | Ann Arbor | |

# Short Gut Syndrome

### Definition
- reduced surface area (length) of small bowel causing insufficient intestinal absorption leading to diarrhea, malnutrition, and dehydration

### Etiology
- acute mesenteric ischemia: resection of large amount of bowel at once
- Crohn's disease: cumulative resections
- malignancies

### Prognostic Factors
- residual small bowel length, residual colon length (reabsorption of water and electrolytes and some reabsorption of nutrients), condition of the remnant small bowel (healthier bowel facilitate better reabsorption), presence of ileocecal valve (delay transition into colon leading to more reabsorption)
- resection of ileum is less tolerated than resection of jejunum (ileum reabsorbs bile salt and vitamin B12)

### Therapy
- medical
  - TPN: replenish lost fluid and electrolytes in diarrhea
  - HT2R antagonist or PPI to prevent gastric acid secretion
  - antimotility agent to prolong transit time in the small intestine
  - consider octreotide to decrease GI secretion and cholestyramine for bile acid absorption
- surgical: non-transplant
  - to slow transit time: small bowel segmental reversal, intestinal valve construction, or electrical pacing of small bowel
  - to increase intestinal length:
    - LILT (longitudinal intestinal lengthening and tailoring) procedure
    - STEP (serial transverse enteroplasty procedure) in dilated small bowels
- surgical: transplant
  - indication: life-threatening complication from intestinal failure or long-term TPN, including liver failure, thrombosis of major central veins, recurrent catheter-related sepsis, and recurrent severe dehydration

# Abdominal Hernia

- see *Hiatus Hernia*, GS13

### Definition
- defect in abdominal wall causing abnormal protrusion of intra-abdominal contents

### Epidemiology
- M:F = 9:1
- lifetime risk of developing a hernia: males 20-25%, females 2%
- frequency of occurrence: 50% indirect inguinal, 25% direct inguinal, 8-10% incisional (ventral), 5% femoral, and 3-8% umbilical
- most common surgical disease of males

### Risk Factors
- activities which increase intra-abdominal pressure
  - obesity, chronic cough, asthma, COPD, pregnancy, constipation, bladder outlet obstruction, ascites, and heavy lifting
- congenital abnormality (e.g. patent processus vaginalis, and indirect inguinal hernia)
- previous hernia repair, especially if complicated by wound infection
- loss of tissue strength and elasticity (e.g. hiatus hernia, aging, and repetitive stress)

### Clinical Features
- mass of variable size
- tenderness worse at end of day, relieved with supine position or with reduction
- abdominal fullness, vomiting, constipation
- transmits palpable impulse with coughing or straining

### Investigations
- physical examination usually sufficient
- U/S ± CT (CT required for obturator hernias, internal abdominal hernias, and Spigelian and/or femoral hernias in obese patients)



**Indirect Inguinal Hernias: Rule of 5s**
5% lifetime incidence in males
5x more common than direct inguinal hernias
5-10x more common in males than females
Generally occur by 5th decade of life



**Inguinal Hernias – MD's don't LIe**
**MD: M**edial to the inferior epigastric a. = **D**irect inguinal hernia
**LI: L**ateral to the inferior epigastric a. = **I**ndirect inguinal hernia



**Inguinal Canal Walls = MALT x 2**

| | |
|---|---|
| **2M** Roof | 2 muscles (internal oblique, transversus abdominis) |
| **2A** Ant. wall | 2 aponeuroses (external and internal oblique) |
| **2L** Floor | 2 ligaments (inguinal and lacunar) |
| **2Ts** Post. wall | 2T (transversalis fascia, conjoint tendon) |



**Borders of Hesselbach's Triangle**
- Lateral: inferior epigastric artery
- Inferior: inguinal ligament
- Medial: lateral margin of rectus sheath

## Classification
- complete: hernia sac and contents protrude through defect
- incomplete: partial protrusion through the defect
- internal hernia: sac herniating into or involving intra-abdominal structure
- external hernia: sac protrudes completely through abdominal wall
- strangulated hernia: vascular supply of protruded viscus is compromised (ischemia)
  - requires emergency repair
- incarcerated hernia: irreducible hernia, not necessarily strangulated
- Richter's hernia: only part of bowel circumference (usually anti-mesenteric border) is incarcerated or strangulated so may not be obstructed
  - a strangulated Richter's hernia may self-reduce and thus be overlooked, leaving a gangrenous segment at risk of perforation in the absence of obstructive symptoms
- sliding hernia: part of wall of hernia sac formed by retroperitoneal structure (usually colon)

## Anatomical Types
- groin
  - indirect and direct inguinal, femoral
  - pantaloon: combined direct and indirect hernias, peritoneum draped over inferior epigastric vessels
- epigastric: defect in linea alba above umbilicus
- incisional: ventral hernia at site of wound closure, may be secondary to wound infection
- other: Littre's (involving Meckel's), Amyand's (containing appendix), lumbar, obturator, peristomal, umbilical, Spigelian (ventral hernia through linea semilunaris)

## Complications
- incarceration
- strangulation
  - small, new hernias more likely to strangulate
  - femoral >> indirect inguinal > direct inguinal
  - intense pain followed by tenderness
  - intestinal obstruction, gangrenous bowel, sepsis
  - surgical emergency
  - DO NOT attempt to manually reduce hernia if septic or if contents of hernial sac gangrenous. This will result in reduction of gangrenous contents and subsequent need for laparotomy

## Treatment
- surgical treatment (herniorrhaphy) is only to prevent strangulation and evisceration, for symptomatic relief, for cosmesis; if asymptomatic can delay surgery
- repair may be done open or laparoscopic and may use mesh for tension-free closure
  - avoid mesh for emergent cases with bowel compromise given risk of infection
- most repairs are now done using tension free techniques – a plug in the hernial defect and a patch over it or patch alone
- observation is acceptable for small asymptomatic inguinal hernias

## Post-Operative Complications
- recurrence (15-20%)
  - risk factors: recurrent hernia, age >50, smoking, BMI >25, poor pre-operative functional status (ASA ≥3 – see Anesthesia and Perioperative Medicine, A4), associated medical conditions: type 2 DM, hyperlipidemia, immunosuppression, and any comorbid conditions increasing intra-abdominal pressure
  - less common with mesh/"tension-free" repair
- scrotal hematoma (3%)
  - painful scrotal swelling from compromised venous return of testes
  - deep bleeding: may enter retroperitoneal space and not be initially apparent
  - difficulty voiding
- nerve entrapment
  - ilioinguinal (causes numbness of inner thigh or lateral scrotum)
  - genital branch of genitofemoral (in spermatic cord)
- stenosis/occlusion of femoral vein
  - acute leg swelling
- ischemic colitis



**Shouldice Technique vs. Other Open Techniques for Inguinal Hernia Repair**
Cochrane DB Syst Rev 2012;4:CD001543
**Purpose**: To evaluate the efficacy and safety of the Shouldice technique compared to other non-laparoscopic techniques.
**Results/Conclusions**: 16 RCTs or quasi-randomized RCTs with 2566 hernias (1121 mesh; 1608 non-mesh). The recurrence rate with Shouldice was higher than mesh (OR 3.80, 95% CI 1.99-7.26) but lower than non-mesh (OR 0.62, 95% CI 0.45-0.85). There was no difference in chronic pain or complications. In conclusion, with respect to recurrence rates, Shouldice herniorrhaphy is the best non-mesh technique, although inferior to mesh. However, it is also more time consuming and results in slightly longer post-operative hospital stays.



**Long-Term Results of a Randomized Controlled Trial of a Nonoperative Strategy (Watchful Waiting) for Men With Minimally Symptomatic Inguinal Hernias**
ANN SURG 2013;258:508-514
**Objective**: Ascertaining the long-term crossover (CO) rate in patients with asymptomatic or minimally symptomatic inguinal hernias undergoing watchful-waiting (WW) as their primary treatment modality.
**Background**: A 2006 randomized control trial comparing WW with routine inguinal hernia repair, concluded that WW was an acceptable option in the management of male patients with minimal symptoms [JAMA. 2006;295(3):285-292]. This study analyzes the WW group after 7 years of follow-up.
**Conclusions**: The estimated CO rate for the WW cohort was 68%, while men older than 65 had a rate of 79%. Therefore, while WW is a safe strategy, it is likely that symptoms will progress, and definitive surgical management will be indicated.



**Outcomes of Laparoscopic vs. Open Repair of Primary Ventral Hernias**
JAMA Surg 2013;148:1043-1048
**Purpose**: To compare outcomes (surgical site infection (SSI), hernia recurrence, and bulging) of patients undergoing laparoscopic ventral hernia repair (LVHR) versus open ventral hernia repair (OVHR).
**Results/Conclusions**: 79 patients with LVHR matched to 79 patients with OVHR with mesh with a median follow-up of 56 mo. LVHR was associated with fewer SSIs (7.6% vs. 34.1%) but more cases of bulging (21.5% vs. 1.3%) and port-site hernia (2.5% vs. 0.0%). No differences in recurrence were observed.

# Groin Hernias

**Table 15. Groin Hernias**

| | Direct Inguinal | Indirect Inguinal | Femoral |
|---|---|---|---|
| **Epidemiology** | 1% of all men | Most common hernia in men and women<br>M>F | Affects mostly females |
| **Etiology** | Acquired weakness of transversalis fascia<br>"Wear and tear"<br>Increased intra-abdominal pressure | Congenital persistence of processus vaginalis in 20% of adults | Pregnancy – weakness of pelvic floor musculature<br>Increased intra-abdominal pressure |
| **Anatomy** | Through Hesselbach's triangle<br>**Medial** to inferior epigastric artery<br>Usually does not descend into scrotal sac | Originates in deep inguinal ring<br>Lateral to inferior epigastric artery<br>Often descends into scrotal sac (or labia majora) | Into femoral canal, below inguinal ligament but may override it<br>Medial to femoral vein within femoral canal |
| **Treatment** | Surgical repair | Surgical repair | Surgical repair |
| **Prognosis** | 3-4% risk of recurrence | <1% risk of recurrence | |

**Table 16. Superficial Inguinal Ring vs. Deep Inguinal Ring***

| Superficial Inguinal Ring | Deep Inguinal Ring |
|---|---|
| Opening in external abdominal aponeurosis; palpable superior and lateral to pubic tubercle | Opening in transversalis fascia: palpable superior to mid-inguinal ligament |
| Medial border: medial crus of external oblique aponeurosis | Medial border: inferior epigastric vessels |
| Lateral border: lateral crus of external oblique aponeurosis | Superior-lateral border: internal oblique and transversus abdominis muscles |
| Roof: intercrural fibres | Inferior border: inguinal ligament |

*see *Basic Anatomy Review*, Figure 2, GS3

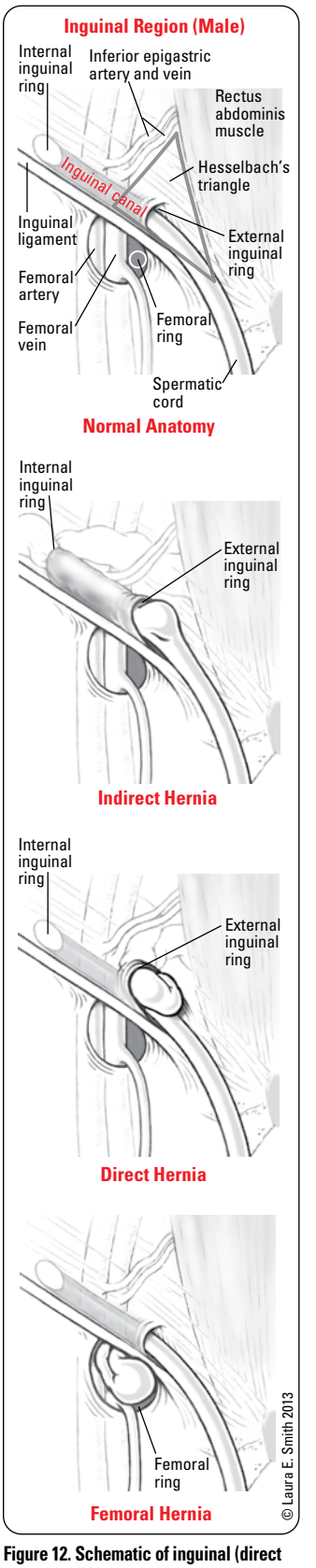



**Figure 12. Schematic of inguinal (direct and indirect) and femoral hernias**

# Appendix

## Appendicitis

### Epidemiology
- 6% of population, M>F
- 80% between 5-35 yr of age

### Pathogenesis
- luminal obstruction → bacterial overgrowth → inflammation/swelling → increased pressure → localized ischemia → gangrene/perforation → localized abscess (walled off by omentum) or peritonitis
- etiology
  - children or young adult: hyperplasia of lymphoid follicles, initiated by infection
  - adult: fibrosis/stricture, fecolith, or obstructing neoplasm
  - other causes: parasites or foreign body

### Clinical Features
- most reliable feature is progression of signs and symptoms
- low grade fever (38°C), rises if perforation
- abdominal pain then anorexia, N/V
- classic pattern: pain initially periumbilical; constant, dull, poorly localized, then well localized pain over McBurney's point
  - due to progression of disease from visceral irritation (causing referred pain from structures of the embryonic midgut, including the appendix) to irritation of parietal structures
- signs
  - inferior appendix: McBurney's sign (see sidebar), Rovsing's sign (palpation pressure to left abdomen causes McBurney's point tenderness). McBurney's sign is present whenever the opening of the appendix at the cecum is directly under McBurney's point; therefore McBurney's sign is present even when the appendix is in different locations
  - retrocecal appendix: psoas sign (pain on flexion of hip against resistance or passive hyperextension of hip)
  - pelvic appendix: obturator sign (flexion then external or internal rotation about right hip causes pain)

### Complications
- perforation (especially if >24 h duration)
- abscess, phlegmon
- sepsis

**McBurney's Sign**
Tenderness 1/3 the distance from the ASIS to the umbilicus on the right side

### Investigations
- laboratory
  - mild leukocytosis with left shift (may have normal WBC counts)
  - higher leukocyte count with perforation
  - β-hCG to rule out ectopic pregnancy
  - urinalysis
- imaging
  - U/S: may visualize appendix, but also helps rule out gynecological causes – overall accuracy 90-94%, can rule in but CANNOT rule out appendicitis (if >6 mm, SENS/SPEC/NPV/PPV 98%)
  - CT scan: thick wall, enlarged (>6 mm), wall enhancement, appendicolith, and inflammatory changes – overall accuracy 94-100%, optimal investigation

### Treatment
- hydrate, correct electrolyte abnormalities
- appendectomy (gold standard)
  - laparoscopic vs. open (see sidebar)
  - complications: intra-abdominal abscess, appendiceal stump leak
  - perioperative antibiotics:
- cefazolin + metronidazole if uncomplicated peri-operative dose is adequate
- consider treatment with post-operative antibiotics for perforated appendicitis
- for patients who present with an abscess (palpable mass or phlegmon on imaging and often delayed diagnosis with symptoms for >4-5 d), consider radiologic drainage + antibiotics x 14 d ± interval appendectomy once inflammation has resolved = (controversial)
- recent research supports antibiotic only treatment as reasonable for uncomplicated appendicitis, with 10-20% recurrence rates
- colonoscopy in the elderly to rule out other etiology (neoplasm)

### Prognosis
- mortality rate: 0.08% (non-perforated), 0.5% (perforated appendicitis)

## Inflammatory Bowel Disease

- see Gastroenterology, G22

### Principles of Surgical Management
- can alleviate symptoms, address complications, and improve quality of life
- conserve bowel: resect as little as possible to avoid short gut syndrome
- perioperative management
  - optimize medical status: may require TPN (especially if >7 d NPO) and bowel rest
  - hold immunosuppressive therapy pre-operative, provide pre-operative stress dose of corticosteroid; if patient had recent steroid therapy, taper steroids post-operative
  - VTE prophylaxis: LMWH or heparin (IBD patients at increased risk of thromboembolic events)

## Crohn's Disease

- see Gastroenterology, G24

### Treatment
- surgery is for symptom management, it is NOT curative, but over lifetime ~70% of Crohn's patients will have surgery
- indications for surgical management
  - failure of medical management
  - SBO (due to stricture/inflammation): indication in 50% of surgical cases
  - abscess, fistula (enterocolic, vesicular, vaginal, cutaneous abscess), quality of life, perforation, hemorrhage, chronic disability, failure to thrive (children), and perianal disease
- surgical procedures
  - resection and anastomosis/stoma if active or subacute inflammation, perforation, or fistula
- resection margin only has to be free of gross disease (microscopic disease irrelevant to prognosis)
  - stricturoplasty – widens lumen in chronically scarred bowel: relieves obstruction without resecting bowel (contraindicated in acute inflammation)

### Complications of Treatment
- short gut syndrome (diarrhea, steatorrhea, malnutrition)
- fistulas
- gallstones (if terminal ileum resected, decreased bile salt resorption → increased cholesterol precipitation)
- kidney stones (loss of calcium in diarrhea → increased oxalate absorption and hyperoxaluria → stones)

### Prognosis
- recurrence rate at 10 yr: ileocolic (25-50%), small bowel (50%), colonic (40-50%)
- re-operation at 5 yr: primary resection (20%), bypass (50%), stricturoplasty (10% at 1 yr)
- 80-85% of patients who need surgery lead normal lives
- mortality: 15% at 30 yr

**Laparoscopic vs. Open Appendectomy**
Cochrane DB Syst Rev 2010;10:CD001546
**Laparoscopic Surgery**
- Wound infection less likely
- Intra-abdominal abscesses 2x more likely
- Reduced pain on POD #1
- Reduced hospital stay by 1.1 d
- Sooner return to normal activity, work, and sport
- Costs outside hospital are reduced

**Open Surgery**
- Shorter duration of surgery
- Lower operation costs

**Overview**
Diagnostic laparoscopy and laparoscopic appendectomy appear to be advantageous over open appendectomy, particularly for young female patients and obese patients.

**Effect of Delay to Operation on Outcomes in Adults with Acute Appendicitis**
Arch Surg 2010;145:886-892
**Purpose**: To examine the effect of delay to appendectomy on morbidity and mortality among adults with appendicitis.
**Method**: Retrospective cohort study with the main exposure being time to operation, and main outcomes being 30 d overall morbidity and serious morbidity/mortality.
**Results**: Of 32,782 patients in the study, 75.2%, 15.1%, and 9.8% underwent surgeries within 6 h, 6-12 h, and >12 h of admission, respectively. Differences in operative duration and length of post-operative stay were statistically significant but not clinically meaningful. No significant differences were observed in adjusted overall morbidity or serious morbidity/mortality. Duration from surgical admission to anesthesia induction was not predictive in regression models for either outcomes.
**Conclusions**: Delay of appendectomy for acute appendicitis among adults does not adversely affect outcomes.

**Antibiotics vs. Placebo for Prevention of Post-Operative Infection After Appendectomy**
Cochrane DB Syst Rev 2005;3:CD001439
**Purpose**: To determine the effectiveness of antibiotics against post-operative infections after appendectomy.
**Method**: Meta-analysis of randomized controlled trials (RCTs) and controlled clinical trials (CCTs), on both adults and children, in which any antibiotic regime was compared to placebo in patients undergoing appendectomy for suspected appendicitis. The main outcomes of interest were wound infection, intra-abdominal abscess, length of hospital stay, and mortality.
**Results**: 45 studies (n=9576) were included. Treatment with antibiotics decreased wound infection and abscess rates.
**Conclusion**: Various prophylactic antibiotic regimens are effective in preventing post-operative complications after appendectomy.

**Crohn's 3 Major Patterns**
- Ileocecal 40% (RLQ pain, fever, weight loss)
- Small intestine 30% (especially terminal ileum)
- Colon 25% (diarrhea)

**Findings in Crohn's**
- "Cobblestoning" on mucosal surface due to edema and linear ulcerations
- "Skip lesions": normal mucosa in between
- "Creeping fat": mesentery infiltrated by fat
- Granulomas: 25-30%

# Ulcerative Colitis

- see Gastroenterology, G24

### Treatment
- indications for surgical management
  - failure of medical management (including inability to taper steroids)
  - complications: hemorrhage, obstruction, perforation, toxic megacolon (emergency), failure to thrive (children)
  - reduce cancer risk (1-2% risk per yr after 10 yr of disease)
- surgical procedures
  - proctocolectomy and ileal pouch-anal anastomosis (IPAA) ± rectal mucosectomy (operation of choice)
  - proctocolectomy with permanent end ileostomy (if not a candidate for ileoanal procedures)
  - colectomy and IPAA ± rectal mucosectomy
  - in emergency: total colectomy and ileostomy with Hartmann closure of the rectum, rectal preservation

### Complications of Treatment
- early: bowel obstruction, transient urinary dysfunction, dehydration (high stoma output), anastomotic leak
- late: stricture, anal fistula/abscess, pouchitis, poor anorectal function, reduced fertility

### Prognosis
- mortality: 5% over 10 yr
- total proctocolectomy will eliminate risk of cancer
- perforation of the colon is the leading cause of death from ulcerative colitis

# LARGE INTESTINE

# Large Bowel Obstruction

## Mechanical Large Bowel Obstruction

### Etiology

**Table 17. Common Causes of LBO**

| Intraluminal | Intramural | Extramural |
|---|---|---|
| Constipation<br>Foreign bodies | Adenocarcinoma<br>Diverticulitis (edema, stricture)<br>IBD stricture<br>Radiation stricture | Volvulus<br>Adhesions<br>Hernias (sigmoid colon in a large groin hernia) |

**Top 3 Causes of LBO (in order)**
- Cancer (>60%)
- Volvulus (10-15%)
- Diverticulitis (10%)

### Clinical Features (unique to LBO)
- open loop (10-20%)
  - incompetent ileocecal valve allows relief of colonic pressure as contents reflux into ileum, therefore clinical feature similar to SBO
- closed loop (80-90%) (dangerous)
  - competent ileocecal valve, resulting in proximal and distal occlusions
  - massive colonic distention → increased pressure in cecum → bowel wall ischemia → necrosis → perforation

**In a patient with clinical LBO consider impending perforation when:**
- Cecum ≥12 cm in diameter
- Tenderness present over cecum

### Treatment
- supportive management: IV fluids, gastrointestinal decompression; 75% require surgical intervention
- surgical correction of obstruction (usually requires resection + temporary diverting colostomy)
- volvulus: initial decompression with flexible sigmoidoscopy, operative reduction or sigmoid resection dependent on severity
- mechanical obstruction: ostomy alone (fecal diversion), colectomy with primary anastomosis or Hartmann procedure. May pursue stenting as bridging (follow with another intervention) or palliation

### Prognosis
- overall mortality: 10%
- cecal perforation + feculent peritonitis: 20% mortality

**Table 18. Bowel Obstruction vs. Paralytic Ileus**

| | SBO | LBO | Paralytic Ileus |
|---|---|---|---|
| **N/V** | Early, may be bilious | Late, may be feculent | Present |
| **Abdominal Pain** | Colicky | Colicky | Minimal or absent |
| **Abdominal Distention** | + (prox SBO), ++ (distal SBO) | ++ | + |
| **Constipation** | + | + | + |
| **Bowel Sounds** | Normal, increased<br>Absent if secondary ileus (delayed presentation) | Normal, increased (borborygmi)<br>Absent if secondary ileus (delayed presentation) | Decreased, absent |
| **AXR Findings** | Air-fluid levels<br>"Ladder" pattern (plicae circularis)<br>Proximal distention (>3 cm) + no colonic gas | Air-fluid levels<br>"Picture frame" appearance<br>Proximal distention + distal decompression<br>No small bowel air if competent ileocecal valve<br>Coffee bean sign (sigmoid volvulus) | Air throughout small bowel and colon |

# Functional LBO: Colonic Pseudo-Obstruction (Ogilvie's Syndrome)

## Definition
- acute pseudo-obstruction
- distention of colon without mechanical obstruction in distal colon
- exact mechanism unknown, likely autonomic motor dysregulation → possibly sympathetic deprivation to colon, unopposed parasympathetic tone, and interruption of sacral parasympathetic tone to distal bowel

## Associations
- most common: trauma, infection, and cardiac (MI, CHF)
- disability (long-term debilitation, chronic disease, bed-bound nursing home patients, and paraplegia), drugs (narcotic use, laxative abuse, and polypharmacy), other (recent orthopedic or neurosurgery, post-partum, electrolyte abnormalities including hypokalemia, retroperitoneal hematoma, and diffuse carcinomatosis)

## Clinical Features
- classically presents with abdominal distention (acute or gradual over 3-7 d)
- abdominal pain, nausea and vomiting, constipation/diarrhea
- watch out for fever, leukocytosis, and presence of peritoneal signs

## Investigations
- AXR: cecal dilatation – if diameter ≥12 cm, increased risk of perforation

## Treatment
- treat underlying cause
- NPO, NGT
- decompression: rectal tube, colonoscopy, neostigmine (cholinergic drug), surgical decompression (ostomy/resection) uncommon
- surgery (extremely rare): if perforation, ischemia, or failure of conservative management

## Prognosis
- most resolve with conservative management

# Diverticular Disease

### Definitions
- diverticulum: abnormal outpouching from the wall of a hollow organ
- diverticulosis: presence of multiple diverticula
- diverticulitis: inflammation of diverticula
- true (congenital) diverticuli: contain all layers of colonic wall, often right-sided
- false (acquired) diverticuli: contain mucosa and submucosa, often left-sided

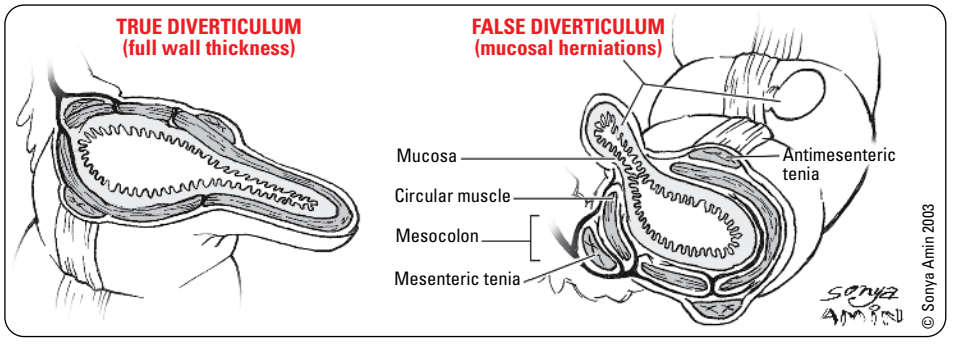



**Figure 13. Diverticular disease – cross-sections of true and false diverticuli**

**Diverticulosis vs. Diverticulitis**
Diverticulosis represents the presence of diverticuli (bulging pouches) within the colonic wall, whereas diverticulitis is the inflammation of one or more diverticuli

## Diverticulosis

### Epidemiology
- 5-50% of Western population, lower incidence in non-Western countries, M=F
- prevalence is age dependent: <5% by age 40, 30% by age 60, 65% by age 85
- 95% involve sigmoid colon (site of highest pressure)

### Pathogenesis
- risk factors
  - lifestyle: low-fibre diet (predispose to motility abnormalities and higher intraluminal pressure), inactivity, and obesity
  - muscle wall weakness from aging and illness (e.g. Ehlers-Danlos, Marfan's)
- high intraluminal pressures cause outpouching to occur at point of greatest weakness, most commonly where vasa recta penetrate the circular muscle layer, therefore increased risk of hemorrhage

### Clinical Features
- uncomplicated diverticulosis: asymptomatic (70-80%)
- episodic abdominal pain (often LLQ), bloating, flatulence, constipation, diarrhea
- absence of fever/leukocytosis
- no physical exam findings or poorly localized LLQ tenderness
- complications
  - diverticulitis (15-25%): 25% of which are complicated (i.e. abscess, obstruction, perforation, fistula)
  - bleeding (5-15%): PAINLESS rectal bleeding, 30-50% of massive LGIB
  - diverticular colitis (rare): diarrhea, hematochezia, tenesmus, and abdominal pain

### Treatment
- uncomplicated diverticulosis: high fibre, education
- diverticular bleed
  - initially workup and treat as any LGIB
  - if hemorrhage does not stop, resect involved region

## Diverticulitis

### Epidemiology
- 95% left-sided in patients of Western countries, 75% right-sided in Asian populations

### Pathogenesis
- erosion of the wall by increased intraluminal pressure or inspissated food particles → inflammation and focal necrosis → micro or macroscopic perforation
- usually mild inflammation with perforation walled off by pericolic fat and mesentery; abscess, fistula, or obstruction can ensue
- poor containment results in free perforation and peritonitis

## Clinical Features

- depend on severity of inflammation and whether or not complications are present; hence ranges from asymptomatic to generalized peritonitis
- LLQ pain/tenderness (2/3 of patients) often for several days before admission
- constipation, diarrhea, N/V, and urinary symptoms (with adjacent inflammation)
- low-grade fever, mild leukocytosis common, and occult or gross blood in stool rarely coexist with acute diverticulitis
- complications (25% of cases)
  - abscess: palpable, tender abdominal mass
  - fistula: colovesical (most common), coloenteric, colovaginal, and colocutaneous
  - colonic obstruction: due to scarring from repeated inflammation
  - perforation: generalized peritonitis (feculent vs. purulent)
- recurrent attacks rarely lead to peritonitis

## Investigations

- CT scan (test of choice): very useful for assessment of severity and prognosis; usually done with rectal contrast
  - 97% sensitive, 99% specific
  - increased soft tissue density within pericolic fat secondary to inflammation, diverticula secondary to inflammation, bowel wall thickening, soft tissue mass (pericolic fluid, abscesses), and fistula
  - 10% of diverticulitis cannot be distinguished from carcinoma
- AXR, upright CXR
  - localized diverticulitis (ileus, thickened wall, SBO, and partial colonic obstruction)
  - free air may be seen in 30% with perforation and generalized peritonitis
- elective evaluation: establish extent of disease and rule out other diagnoses (polyps and malignancy) AFTER resolution of acute episode
  - colonoscopy or barium enema and flexible sigmoidoscopy

## Treatment

- uncomplicated: conservative management
- outpatient: clear fluids only until improvement and antibiotics (e.g. ciprofloxacin and metronidazole) 7-10 d to cover Gram negative rods and anaerobes (e.g. *B. fragilis*)
- hospitalize: if severe presentation, inability to tolerate oral intake, significant comorbidities, or fail to improve outpatient management
- treat with NPO, IVF, and IV antibiotics (e.g. IV ceftriaxone + metronidazole)
- image-guided (CT) percutaneous drainage of abscesses reduces the urgency of surgical resection in most patients
- indications for surgery
  - unstable patient with peritonitis
  - Hinchey stage 3-4 (see Table 19)
  - after 1 attack if immunosuppressed
  - consider if recurrent episodes of diverticulitis (3 or more), recent trend is toward conservative management of recurrent mild/moderate attacks
  - complications: perforation, abscess, fistula, obstruction, hemorrhage, inability to rule out colon cancer on endoscopy, or failure of medical management
- surgical procedures
  - for unstable patient or complex cases: Hartmann procedure
- colon resection + colostomy and rectal stump → colostomy reversal in 3-6 mo
  - for more stable patients with Hinchey stage 3 and 4 acute diverticulitis, colonic resection, primary anastomosis + diverting loop ileostomy is becoming more common, with benefits for mortality and morbidity
  - laparoscopic peritoneal lavage with drain placement near the affected colon, in addition to 4 antibiotics (NO resection) has been proposed for Hinchey stage 3

## Prognosis

- mortality rates: 6% for purulent peritonitis, 35% for feculent peritonitis
- recurrence rates: 13-30% after first attack, 30-50% after second attack

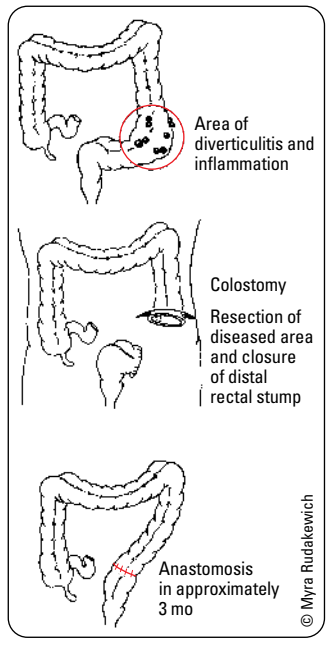



**Figure 14. Hartmann procedure**

**Table 19. Hinchey Staging and Treatment for Diverticulitis**

| Hinchey Stage | Description | Acute Treatment |
|---|---|---|
| 1 | Phlegmon/small pericolic abscess | Medical |
| 2 | Large abscess/fistula | Medical, abscess drainage ± resection with primary anastomosis |
| 3 | Purulent peritonitis (ruptured abscess) | Resection or Hartmann procedure |
| 4 | Feculent peritonitis | Hartmann procedure |

# Colorectal Neoplasms

## Colorectal Polyps

### Definition
- polyp: protuberance into the lumen of normally flat colonic mucosa
- sessile (flat) or pedunculated (on a stalk)

### Epidemiology
- 30% of the population have polyps by age 50, 40% by age 60, 50% by age 70; M>F

### Clinical Features
- 50% in the rectosigmoid region, 50% are multiple
- usually asymptomatic, do not typically bleed, tenesmus, intestinal obstruction, and mucus
- usually detected during routine endoscopy or familial/high risk screening

### Pathology
- non-neoplastic/non-adenomatous
  - hyperplastic: most common non-neoplastic polyp
  - mucosal polyps: small <5 mm, no clinical significance
  - hamartomas: juvenile polyps (large bowel), Peutz-Jegher syndrome (small bowel)
    - malignant risk due to associated adenomas (large bowel)
    - low malignant potential → most spontaneously regress or autoamputate
  - inflammatory pseudopolyps: associated with IBD, no malignant potential
  - submucosal polyps: lymphoid aggregates, lipomas, leiomyomas, and carcinoids
- neoplastic/adenomatous
  - adenomas: premalignant, considered carcinoma in situ if high grade dysplasia
    - some may contain invasive carcinoma ("malignant polyp" – 3-9%): invasion into submucosa
    - malignant potential related to histological type: villous > tubulovillous > tubular

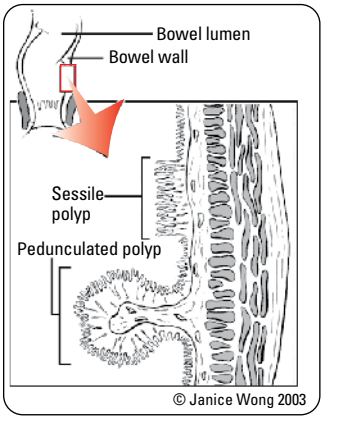



**Figure 15. Sessile and pedunculated polyps**

**Table 20. Characteristics of Tubular vs. Villous Polyps**

| | Tubular | Villous |
|---|---|---|
| **Incidence** | Common (60-80%) | Less common (10%) |
| **Size** | Small (<2 cm) | Large (usually >2 cm) |
| **Attachment** | Pedunculated | Sessile |
| **Malignant Potential** | Lower | Higher |
| **Distribution** | Even | Left-sided predominance |

### Investigations
- colonoscopy with biopsy/resection is the gold standard for diagnosis and treatment of colonic polyps
- CT colonography: increasing in availability; patients still require bowel prep and will require colonoscopy if polyps are identified
- other: flexible sigmoidoscopy if polyps are detected, proceed to colonoscopy for examination of entire bowel and biopsy

### Treatment
- indications: symptoms, malignancy or risk of malignancy (i.e. adenomatous polyps)
- endoscopic removal of entire growth
- indications for segmental resection for malignant polyps: 1) lymphovascular invasion; 2) tumour budding; 3) positive resection margin; 4) poorly differentiated cells; 5) evidence of regional or distant metastases on staging. Most of these cases are usually discussed at multi-disciplinary tumour boards
- follow-up endoscopy:
  - every 5 years: if low-risk polyp (<10 mm tubular adenoma or <10 mm sessile serrated without dysplasia)
  - every 3 years: if high-risk polyp (3-10 tubular adenomas, >10 mm tubular or serrated polyp, adenoma with villous features or high grade dysplasia, or sessile serrated with dysplasia)

## Familial Colon Cancer Syndromes

### FAMILIAL ADENOMATOUS POLYPOSIS

### Pathogenesis
- autosomal dominant inheritance, mutation in adenomatous polyposis coli (APC) gene

### Clinical Features
- hundreds to thousands of colorectal adenomas usually by age 20 (by 40s in attenuated FAP)
- extracolonic manifestations
  - carcinoma of large bowel (i.e. polyps in colon), bile duct, pancreas, stomach, thyroid, adrenal, and small bowel
  - congenital hypertrophy of retinal pigment epithelium presents early in life in 2/3 of patients; 97% sensitivity
  - virtually 100% lifetime risk of colon cancer (because of number of polyps)
- variants
  - Gardner's syndrome: FAP + extra-intestinal lesions (sebaceous cysts, osteomas, desmoid tumours)
  - Turcot syndrome: FAP + CNS tumours (childhood cerebellar medulloblastoma)

**Referral Criteria for Genetic Screening for APC**
- To confirm the diagnosis of FAP (in patients with ≥100 colorectal adenomas)
- To provide pre-symptomatic testing for individuals at risk for FAP (1st degree relatives who are ≥10 yr)
- To confirm the diagnosis of attenuated FAP (in patients with ≥20 colorectal adenomas)

### Investigations
- genetic testing (80-95% sensitive, 99-100% specific)
- if no polyposis found: annual flexible sigmoidoscopy from puberty to age 50, then routine screening
- if polyposis or APC gene mutation found: annual colonoscopy and consider surgery; consider upper endoscopy to evaluate for periampullary tumours

**Revised Bethesda Criteria for HNPCC and Microsatellite Instability (MSI)**
Tumours from individuals should be tested for MSI in the following situations:
- Colorectal cancer diagnosed in a patient who is <50 yr
- Presence of synchronous, metachronous, colorectal, or other HNPCC-associated tumours, regardless of age
- Colorectal cancer with the MSI-H histology diagnosed in a patient who is <60 yr
- Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumour, with one of the cancers being diagnosed <50 yr
- Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumours, regardless of age

### Treatment
- surgery indicated by age 17-20
- total proctocolectomy with ileostomy or total colectomy with ileorectal anastomosis
- doxorubicin-based chemotherapy
- NSAIDs for intra-abdominal desmoids

## HEREDITARY NON-POLYPOSIS COLORECTAL CANCER – LYNCH SYNDROME

### Pathogenesis
- autosomal dominant inheritance, mutation in a DNA mismatch repair gene (MSH2, MSH6, MLH1, PMS2) resulting in microsatellite genomic instability and subsequent mutations
- microsatellite instability account for approximately 15% of all colorectal cancers

### Clinical Features
- early age of onset, right > left colon, synchronous and metachronous lesions
- mean age of cancer presentation is 44 yr, lifetime risk 70-80% (M>F)
  - HNPCC I: hereditary site-specific colon cancer
  - HNPCC II: cancer family syndrome – high rates of extracolonic tumours (endometrial, ovarian, hepatobiliary, small bowel)

Elderly persons who present with iron-deficiency anemia should be investigated for colon cancer

### Diagnosis
- Amsterdam Criteria ("3-2-1 rule")
  - 3 or more relatives with verified Lynch syndrome associated cancers, and 1 must be 1st degree relative of the other 2
  - 2 or more generations involved
  - 1 case must be diagnosed before 50 yr
  - FAP is excluded
- genetic testing (80% sensitive) – colonoscopy mandatory even if negative
  - refer for genetic screening individuals who fulfill either the Amsterdam Criteria or the revised Bethesda Criteria
- colonoscopy (starting age 20) annually
- surveillance for extracolonic lesions

### Treatment
- total colectomy and ileorectal anastomosis with annual proctoscopy

# Colorectal Carcinoma

### Epidemiology
- 3rd most common cancer (lung>breast>colon), 2nd most common cause of cancer death

### Risk Factors
- most patients have no specific risk factors
- age >50 (dominant risk factor in sporadic cases), mean age is 70
- genetic: FAP, HNPCC, or family history of CRC
- colonic conditions
  - adenomatous polyps (especially if >1 cm, villous, multiple)
  - IBD (especially UC: risk is 1-2%/yr if UC >10 yr)
  - previous colorectal cancer (also gonadal or breast)
- diet (increased fat, red meat, and decreased fibre) and smoking
- DM and acromegaly (insulin and IGF-1 are growth factors for colonic mucosal cells)

**APR** removes distal sigmoid colon, rectum, and anus; permanent end colostomy required
**LAR** removes distal sigmoid and rectum with anastomosis of distal colon to anus

## Pathogenesis
- adenoma-carcinoma sequence; rarely arise *de novo*

## Clinical Features
- often asymptomatic
- hematochezia/melena, abdominal pain, and change in bowel habits
- others: weakness, anemia, weight loss, palpable mass, and obstruction
- 20% patients have distant metastatic disease at time of presentation
- spread
  - direct extension, lymphatic, and hematogenous (liver most common, lung, bone, and brain; tumour of distal rectum → IVC → lungs)
  - peritoneal seeding: ovary and Blumer's shelf (pelvic cul-de-sac)

**Table 21. Clinical Feature of CRC**

| | Right Colon | Left Colon | Rectum |
|---|---|---|---|
| **Frequency** | 25% | 35% | 30% |
| **Pathology** | Exophytic lesions with occult bleeding | Annular, invasive lesions | Ulcerating |
| **Symptoms** | Weight loss, weakness, rarely obstruction | Constipation ± overflow (alternating bowel patterns), abdominal pain, decreased stool calibre, rectal bleeding | Obstruction, tenesmus, rectal bleeding |
| **Signs** | Fe-deficiency anemia, RLQ mass (10%) | BRBPR, LBO | Palpable mass on DRE, BRBPR |

## Investigations
- colonoscopy (best), look for synchronous lesions (3-5% of patients); alternative: air contrast barium enema ("apple core" lesion) + sigmoidoscopy
- if a patient is FOBT +ve, has microcytic anemia, or has a change in bowel habits, do colonoscopy
- laboratory: CBC, urinalysis, liver enzymes, liver function tests, CEA (pre-operative for baseline, >5 ng/mL have worse prognosis)
- staging: CT chest/abdomen/pelvis; bone scan, CT head only if lesions suspected
- rectal cancer: pelvic MRI or endorectal U/S to determine T and N stage

**Table 22. TNM Classification System for Staging of Colorectal Carcinoma (AJCC/UICC 8th edition)**

| Primary Tumour (T) | | Regional Lymph Nodes (N) | | Distant Metastasis (M) | |
|---|---|---|---|---|---|
| **Tx** | Primary tumour cannot be assessed | **Nx** | Regional nodes cannot be assessed | **M0** | No distant metastasis |
| **T0** | No primary tumour found | **N0** | No regional node metastasis and no tumour deposits | **M1a** | Distant metastasis to 1 organ or site and no peritoneal metastasis |
| **Tis** | Carcinoma *in situ*, limited to intraepithelial or invasive lamina propria | **N1a** | Metastasis in 1 regional node | **M1b** | Distant metastasis to >1 (2 or more organs sites) and no peritoneal metastasis |
| **T1** | Invasion into submucosa | **N1b** | Metastasis in 2-3 regional nodes | **M1c** | Metastasis to peritoneal surface |
| **T2** | Invasion into muscularis propria | **N1c** | No regional node metastasis; tumour deposits were submucosal, mesangial or peritoneum-covered para-colorectal tissue | | |
| **T3** | Invasion through muscularis propria and into pericolorectal tissues | **N2a** | Metastasis in 4-6 regional nodes | | |
| **T4a** | Invasion through visceral peritoneum | **N2b** | Metastasis in ≥7 regional nodes | | |
| **T4b** | Invasion or adherent to other organs or structures | | | | |

## Treatment
- colon cancer
  - wide surgical resection of lesion and regional lymphatic drainage; usually colectomy with primary anastomosis
- curative: wide resection of lesion (5 cm margins) with nodes (>12) and mesentery
- metastatic lesions confined to the liver can be resected with curative intent
- palliative: if distant spread, local control for hemorrhage or obstruction
- care is taken to not spread tumour by unnecessary palpation
- cancer-bearing portion of colon is removed according to vascular distribution of segment
  - adjuvant chemotherapy (oxaliplatin-based ± capecitabine, fluorouracil) for stage III and is considered in select stage II patients

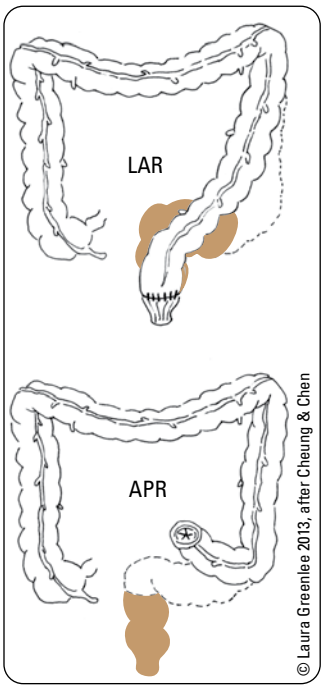



**Figure 16. APR vs. LAR**

**5 Year Survival Rates for CRC**

| Stage | 20-64 yr | ≥65 yr |
|---|---|---|
| I | 95.2% | 89.1% |
| IIA | 89.6% | 84.4% |
| IIB | 67.6% | 55% |
| IIIA | 91.3% | 85.1% |
| IIIB | 76.9% | 64.6% |
| IIIC | 61.8% | 45.5% |
| IV | 14.2% | 7.4% |

**Pre-Operative vs. Post-Operative Chemoradiotherapy for Locally Advanced Rectal Cancer: Results of the German CAO/ARO/AIO-94 Randomized Phase III Trial after a Median Follow-Up of 11 Yr**

J Clin Oncol 2012;30:1926-33

**Background**: The CAO/ARO/AIO-94 trial (published 2004) recommended pre-operative chemoradiotherapy (CRT) as standard treatment for locally advanced rectal cancer. However, no survival benefit was shown after median follow-up of 46 mo, and this study reports long-term effects.

**Methods**: Patients with stage II to III rectal cancer (n=799) were randomly assigned to pre-operative (n=404) or post-operative CRT (n=395) with fluorouracil (FU), radiation, and adjuvant FU chemotherapy, in addition to total mesorectal excision surgery. Follow-up was designed to assess long-term overall survival as the primary end point and cumulative incidence of local and distant relapses as well as disease-free survival as secondary end points.

**Results**: 10 yr incidence of local relapse was significantly lower in the pre-operative CRT group than in the post-operative group (7.1% vs. 10.1%, p=0.048). Overall survival at 10 yr was similar at ~60% for patients treated with pre-operative or post-operative CRT (p=0.85). Disease-free survival rates at 10 yr was similar at ~68% for patients treated with pre-operative or post-operative CRT (p=0.54). No significant difference was detected for 10 yr incidence of distant metastases (pre-operative CRT 29.8% vs. post-operative CRT 29.6%, p=0.9).

**Conclusion**: There is long-term reduction in local recurrence of stage II to III rectal cancer with pre-operative chemotherapy, but no improvement in overall survival or distant recurrence of disease.

- rectal cancer
  - choice of operation depends on individual case; types of operations
- low anterior resection of rectum (LAR): curative procedure of choice if adequate distal margins (~2 cm); uses technique of total mesorectal excision
- abdominoperineal resection of rectum (APR): if adequate distal margins cannot be obtained; involves the removal of distal sigmoid colon, rectum, and anus – permanent end colostomy required
- transanal minimally invasive surgery (TAMIS)- local excision for select T1 lesions only
- palliative procedures involve proximal diversion with an ostomy for obstruction and radiation for bleeding or pain
  - adjuvant therapy
- combined neoadjuvant chemoradiation therapy followed by post-operative adjuvant chemotherapy for stages II and III

### Follow-Up
- stage I: mixed recommendations; either routine colonoscopy or screening like stage II & III
- stage II & III: regular follow-up q3-6mo for 3 yr, then q6mo until 5 yr, with regular measurement of serum CEA for at least 3 yr; annual CT chest/abdo/pelvis for at least 3 yr; colonoscopy at 1, 3 and 5 yr
- stage IV: no data on surveillance strategy

# Other Conditions of the Large Intestine

## Angiodysplasia

### Definition
- vascular malformation: focal submucosal venous dilatation and tortuosity

### Clinical Features
- most frequently in right colon of patients >60 yr
- predisposition in end-stage renal disease and von Willebrand disease
- bleeding typically intermittent, rarely massive, and not usually hypotensive (melena, anemia, and occult blood positive stools)

### Investigations
- colonoscopy: cherry red spots, branching pattern from central vessel
- angiography: early-filling vein, vascular tuft, and delayed emptying vein; rarely active bleeding
- RBC technetium-99 scan
- barium enema is contraindicated (obscures other x-rays, i.e. angiogram)

### Treatment
- none if asymptomatic
- cautery, right hemicolectomy, embolization, vasopressin infusion, sclerotherapy, band ligation, laser, octreotide, and rarely segmental resection if other treatments fail

## Volvulus

### Definition
- rotation of segment of bowel about its mesenteric axis
- sigmoid (65%), cecum (30%), transverse colon (3%), and splenic flexure (2%)
- 5-10% of large bowel obstruction; 25% of intestinal obstruction during pregnancy



**Cecal Volvulus**
AXR: Central cleft of "coffee bean" sign points to RLQ



**Sigmoid Volvulus**
**AXR:** Central cleft of "coffee bean" sign points to LLQ
**Barium enema:** "ace of spades" or "bird's beak" sign

### Risk Factors
- age (50% of patients >70 yr: stretching/elongation of bowel with age is a predisposing factor)
- high fibre diet (can cause elongated/redundant colon), chronic constipation, laxative abuse, pregnancy, bedridden, and institutionalization (less frequent evacuation of bowels)

### Clinical Features
- symptoms due to bowel obstruction (see *Large Bowel Obstruction*, GS34) or intestinal ischemia (see *Intestinal Ischemia*, GS28)
- colicky abdominal pain, persistence of pain between spasms, abdominal distention, and vomiting

### Investigations
- AXR (classic findings): "omega", "bent inner-tube", "coffee-bean" signs
- barium/Gastrografin® enema: "ace of spades" (or "bird's beak") appearance due to funnel-like luminal tapering of lower segment towards volvulus
- sigmoidoscopy or colonoscopy as appropriate
- CT: "whirl pattern" of mesenteric vessels twisting about the volvulus axis

### Treatment
- initial supportive management same as initial management for bowel obstruction (see *Large Bowel Obstruction*, GS34)

- cecum
  - nonsurgical
    - may attempt colonoscopic detorsion and decompression; successful 15-20% of cases
  - surgical
    - right colectomy + ileotransverse colonic anastomosis
- sigmoid
  - nonsurgical
    - decompression by flexible sigmoidoscopy and insertion of rectal tube past obstruction
    - subsequent elective surgery recommended (50-70% recurrence)
  - surgical
    - surgical resection with or without primary anastomosis
    - indications: strangulation, perforation, or unsuccessful endoscopic decompression

# Toxic Megacolon

### Pathogenesis
- extension of inflammation into smooth muscle layer causing paralysis
- damage to myenteric plexus and electrolyte abnormalities are not consistently found

### Etiology
- inflammatory bowel disease (ulcerative colitis > Crohn's disease)
- infectious colitis: bacterial (*C. difficile, Salmonella, Shigella*, and *Campylobacter*), viral (cytomegalovirus), and parasitic (*E. histolytica*)

### Clinical Features
- infectious colitis usually presents for >1 wk before colonic dilatation
- diarrhea ± blood (sudden improvement of diarrhea may signify onset of megacolon)
- abdominal distention, tenderness, ± local/general peritoneal signs (suggests perforation)
- triggers: hypokalemia, constipating agents (opioids, antidepressants, loperamide, and anticholinergics), barium enema, and colonoscopy

### Diagnostic Criteria
- must have both colitis and systemic manifestations for diagnosis
- radiologic evidence of dilated colon
- three of: fever, HR >120, WBC >10.5, and anemia
- one of: fluid and electrolyte disturbances, hypotension, or altered LOC

### Investigations
- CBC (leukocytosis with left shift and anemia from bloody diarrhea), electrolytes, elevated CRP, and ESR
- metabolic alkalosis (volume contraction and hypokalemia) and hypoalbuminemia are late findings
- AXR: dilated colon >6 cm (right > transverse > left), loss of haustra
- CT: useful to assess underlying disease

### Treatment
- NPO, NGT, stop constipating agents, correct fluid and electrolyte abnormalities, and transfusion
- serial AXRs
- broad-spectrum antibiotics (reduce sepsis and anticipate perforation)
- aggressive treatment of underlying disease (e.g. steroids in IBD and metronidazole for *C. difficile*)
- indications for surgery (50% improve on medical management)
  - worsening or persisting toxicity or dilation after 48-72 h
  - severe hemorrhage, perforation
  - high lactate and WBC, especially for *C. difficile*
- procedure: subtotal colectomy + end ileostomy (may be temporary with second operation for re-anastomosis later)



Use caution when giving antidiarrheal agents, especially with bloody diarrhea

### Prognosis
- 25-30% mortality

# Fistula

### Definition
- abnormal communication between two epithelialized surfaces (e.g. enterocutaneous, colovesical, aortoenteric, and entero-enteric)

### Etiology
- foreign object erosion (e.g. gallstone, graft)
- inflammatory states (e.g. infection, IBD [Crohn's > UC], and diverticular disease)
- iatrogenic/surgery (e.g. post-operative anastomotic leak and radiation)
- congenital, trauma
- neoplastic



**Why Fistulae Stay Open**

**FRIENDO**
**F**oreign body
**R**adiation
**I**nfection
**E**pithelialization
**N**eoplasm
**D**istal obstruction (most common)
**O**thers: increased flow; steroids (may inhibit closure, usually will not maintain fistula)

### Investigations
- U/S, CT scan, fistulogram
- measure amount of drainage from fistula

### Treatment
- decrease secretion: octreotide/somatostatin/omeprazole
- surgical intervention: dependent upon etiology (for non-closing fistulas); uncertainty of diagnosis

## Stomas

### Definition
- an opening of the GI tract onto the surface of the abdomen wall
  - stomas can be constructed as either end stomas: the proximal end of the GI tract forms the stoma and the distal end of the GI tract is not part of the stoma
  - loop stomas: a loop of the GI tract is brought up to the skin and the anti-mesenteric surface of the bowel is matured as a stoma
- the proximal and distal GI tract remain in continuity

**Colostomy/Ileostomy**
- Connection of proximal limb of colon or ileum to abdominal wall skin

**Mucous Fistula**
- Connection of distal limb of colon to abdominal wall skin

**Ileal Conduit**
- Connection of bowel to ureter proximally and abdominal wall distally to drain urine

### Ileostomy
- usually positioned in RLQ; ileum is brought through rectus abdominus muscles
- indications: after protocolectomy for ulcerative colitis, in some cases of Crohn's disease or familial polyposis
- conventional ileostomy: discharges small quantities of liquid material continuously, appliance (plastic bag attached to a sheet of protective material) required at all times
- continent ileostomy: reservoir is constructed from distal ileum, emptied by inserting catheter into stoma several times a day; rarely used, has mostly been replaced by ileal pouch anal anastomosis

### Colostomy
- indications: to decompress an obstructed colon, to protect a distal anastomosis after resection, or to evacuate stool after distal colon or rectum is removed
- colostomies can be done by making an opening in a loop of colon (loop colostomy) or by dividing the colon and bringing out one end (end colostomy)
- most common permanent colostomy is a sigmoid colostomy – expels stool 1/d, no appliance required
- chronic paracolostomy hernia is a common complication

### Complications (10%)
- obstruction: herniation, stenosis (skin and abdominal wall), adhesive bands, volvulus
- peri-ileostomy abscess and fistula
- skin irritation
- prolapse or retraction
- diarrhea (excessive output), which may lead to fluid, electrolyte, and nutritional imbalances

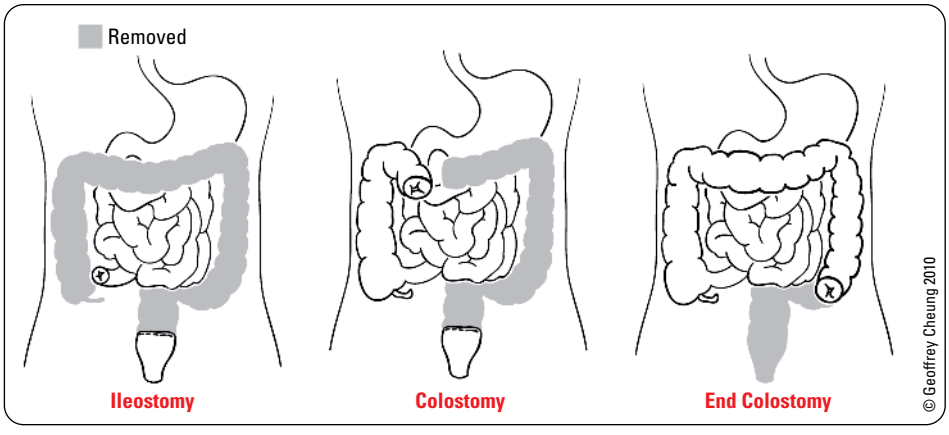



Figure 18. Ostomies

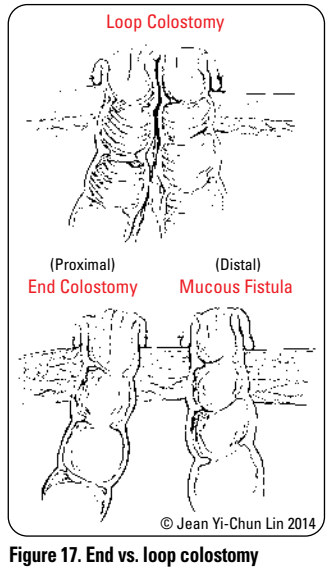



Figure 17. End vs. loop colostomy

# Anorectum

## Hemorrhoids

### Etiology
- vascular and connective tissue complexes form a plexus of dilated veins (cushion)
- internal: superior hemorrhoidal veins, above dentate line, portal circulation
- external: inferior hemorrhoidal veins, below dentate line, systemic circulation

### Risk Factors
- increased intra-abdominal pressure: chronic constipation, pregnancy, obesity, portal HTN, heavy lifting

### Clinical Features and Treatment
- internal hemorrhoids
  - engorged vascular cushions usually at 3, 7, 11 o'clock positions (patient in lithotomy position)
  - painless rectal bleeding, anemia, prolapse, mucus discharge, pruritus, burning pain, and rectal fullness
    - **1st degree**: bleed but do not prolapse through the anus
      - treatment: high fibre/bulk diet, sitz baths, steroid cream (short course), pramoxine (Anusol®), phlebotonics, rubber band ligation, sclerotherapy, and photocoagulation
    - **2nd degree**: bleed, prolapse with straining, and spontaneous reduction
      - treatment: rubber band ligation, and photocoagulation
    - **3rd degree**: bleed, prolapse, and require manual reduction
      - treatment: same as 2nd degree, but may require closed hemorrhoidectomy
    - **4th degree**: bleed, permanently prolapsed, and cannot be manually reduced
      - treatment: closed hemorrhoidectomy
- external hemorrhoids
  - dilated venules usually mildly symptomatic
    - pain after bowel movement, associated with poor hygiene
    - medical treatment: dietary fibre, stool softeners, steroid cream (short course), pramoxine (Anusol®), phlebotonics, and avoid prolonged straining
  - thrombosed hemorrhoids are very painful
    - resolve within 2 wk, may leave excess skin = perianal skin tag
    - treatment: consider surgical decompression within first 48 h of thrombosis, otherwise medical treatment

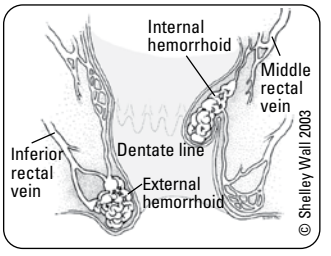



**Figure 19. Hemorrhoids**

Always rule out more serious causes (e.g. colon cancer or anal canal cancer) in a person with hemorrhoids and rectal bleeding

Band ligation can be done as outpatient

External hemorrhoids will often recur

**Table 23. Signs and Symptoms of Internal vs. External Hemorrhoids**

| Internal Hemorrhoids | External Hemorrhoids |
|---|---|
| Painless BRBPR | Sudden severe perianal pain |
| Rectal fullness or discomfort | Perianal mass |
| Mucus discharge | |

## Anal Fissures

### Definition
- tear of anal canal below dentate line (very sensitive squamous epithelium)
- 90% posterior midline, 10% anterior midline
- if off midline: consider other possible causes such as IBD, STIs, TB, leukemia, or anal carcinoma
- repetitive injury cycle after first tear
  - sphincter spasm occurs preventing edges from healing and leads to further tearing
  - ischemia may ensue and contribute to chronicity

### Etiology
- local trauma: constipation, irritation, diarrhea, vaginal delivery, anal intercourse
- secondary to: Crohn's disease, granulomatous diseases, malignancy, communicable diseases
- further tearing by internal anal sphincter spasm and hypertonicity

### Clinical Features
- acute fissure
  - very painful bright red bleeding especially after bowel movement, sphincter spasm on limited DRE
  - treatment is conservative: stool softeners, bulking agents, and sitz baths (heals 90%)
- chronic fissure (anal ulcer)
  - triad: fissure, sentinel skin tags, and hypertrophied papillae
  - treatment
    - stool softeners, increased fibre intake, and sitz baths
    - topical nitroglycerin or calcium channel blocker (nifedipine or diltiazam): increases local blood flow, promotes healing, and relieves sphincter spasm
    - lateral internal anal sphincterotomy (most effective): relieves sphincter spasm to increase blood flow and promote healing; reserved for medically-refractory cases due to 5% chance of fecal incontinence
    - alternative treatment: botulinum toxin A; inhibits release of acetylcholine (ACh), reducing sphincter spasm

# Anorectal Abscess

## Definition
- infection typically originating within an obstructed anal crypt which forms an abscess
- common bacterial: *E. coli, Proteus, Streptococci, Staphylococci, Bacteroides*, and anaerobes

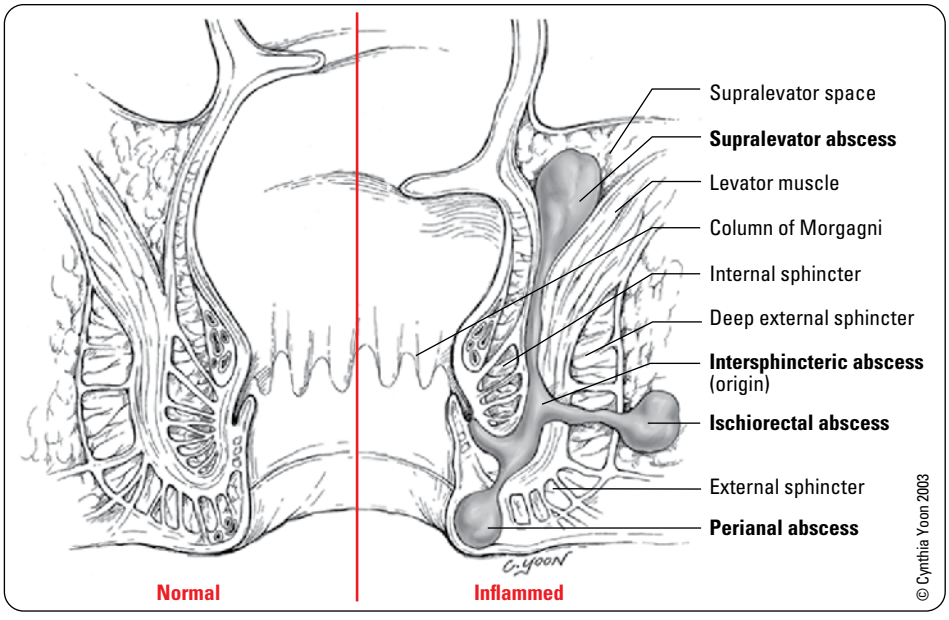



**Figure 20. Different types of perianal abscesses**

## Clinical Features
- throbbing pain that may worsen with straining and ambulation
- abscess can spread vertically downward (perianal), vertically upward (supralevator), or horizontally (ischiorectal)
- tender perianal/rectal mass on exam

## Treatment
- I&D
  - curative in 50% of cases
  - 50% develop anorectal fistulas
- may require antibiotics if diabetic, heart murmur, or cellulitis

Recurrent perianal abscesses is associated with Crohn's disease

Antibiotics are not typically helpful in the treatment of perianal abscesses

# Fistula-In-Ano

## Definition
- fistula from anal canal to perianal skin
- an inflammatory tract with internal os at dentate line, external os on skin

## Etiology
- see *Fistula*, GS42
- same processes that lead to the formation of an anal abscess
- other causes: post-operative, trauma, anal fissure, malignancy, and radiation proctitis

## Clinical Features
- intermittent or constant purulent discharge from perianal opening
- pain
- palpable cord-like tract

## Treatment
- identification
  - internal opening
    - Goodsall's rule
      - fistulas originating anterior to a transverse line through the anus will have a straight course and exit anteriorly, whereas those originating posterior to the transverse line will begin in the midline and have a curved tract
  - fistulous tract
    - probing or fistulography under anesthesia

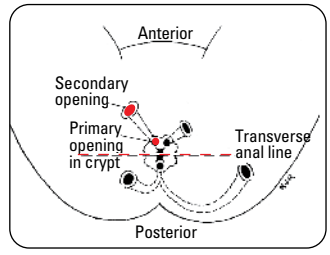



**Figure 21. Goodsall's rule**

- surgery
  - fistulotomy: unroof tract from external to internal opening, allow drainage, heals by secondary intention
  - low lying fistula (does not involve external sphincter) → primary fistulotomy
  - high lying fistula (involves external sphincter) → staged fistulotomy with Seton suture placed through tract
    - promotes drainage
    - promotes fibrosis and decreases incidence of incontinence
    - delineates anatomy
    - usually done to spare muscle
  - alternative for high lying fistula → ligation of intersphicteric fistula tract (LIFT) procedure
    - access fistula between sphincter muscles, sparring them

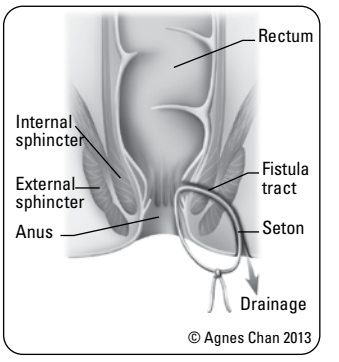


**Figure 22. Fistulotomy**

### Post-Operative
- sitz baths, irrigation, and packing to ensure healing proceeds from inside to outside

### Complications
- recurrence
- rarely fecal incontinence

## Pilonidal Disease

### Definition
- pilo = hair, nidal = nest; cyst or abscess near or on the intergluteal cleft of the sacrococcygeal area containing hair and skin debris

### Epidemiology
- occurs most frequently in young men age 15-35 yr; rare in >50 yr

### Etiology
- obstruction of the hair follicles in this area → formation of cysts, sinuses, or abscesses
- associated with occupations that require prolonged sitting, obesity, and high amounts of body hair

### Clinical Features
- asymptomatic or chronically itchy until acutely infected, then pain/tenderness, purulent discharge, and increased moisture near the tailbone

### Treatment
- acute abscess
  - I&D (often performed by primary care doctors)
  - wound packed open
  - 40% develop chronic pilonidal sinuses
- surgery
  - indication: failure of healing after I&D, recurrent disease, or complex disease
  - pilonidal cystotomy: excision of sinus tract and cyst; wound closed by secondary intention, primary closure with tissue flap, or marsupialization (cyst edge sewn to surrounding tissue to leave sinus tract open)

## Rectal Prolapse

### Definition
- protrusion of some or all of rectal mucosa through external anal sphincter

### Epidemiology
- extremes of ages: <5 yr and >50 yr
- 85% women

### Etiology
- lengthened attachment of rectum secondary to constant straining
- 2 types
  1. false/partial/mucosal: protrusion of mucosa only, radial furrows at junction with anal skin; most common type of rectal prolapse in childhood
  2. true/complete (most common): full thickness extrusion of rectal wall, concentric folds in:
     - first degree: prolapse includes mucocutaneous junction
     - second degree: without involvement of mucocutaneous junction
     - third degree (internal intussusception): prolapse is internal, concealed, or occult

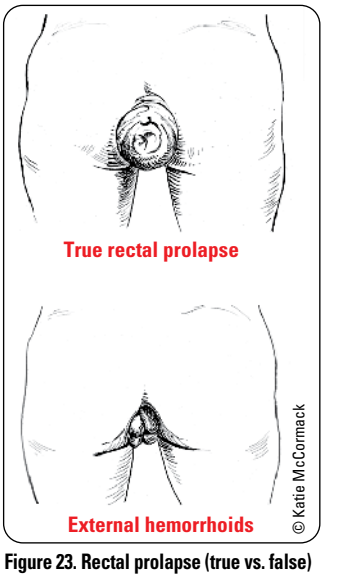


**Figure 23. Rectal prolapse (true vs. false)**

### Risk Factors
- gynecological surgery
- chronic neurologic/psychiatric disorders affecting motility

### Clinical Features
- extrusion of mass with increased intra-abdominal pressure
- difficulty in bowel regulation
  - tenesmus, constipation, fecal incontinence
- permanently extruded rectum with excoriation, ulceration, and constant soiling
- may be associated with urinary incontinence or uterine prolapse

### Treatment
- Type I
  - conservative: gentle manual reduction of prolapsed area, especially in children
  - mucosectomy with excision of redundant mucosa, mostly in adults
- Type II
  - conservative: reduce if possible
  - surgery: abdominal, perineal, and transsacral approaches

# Anal Neoplasms

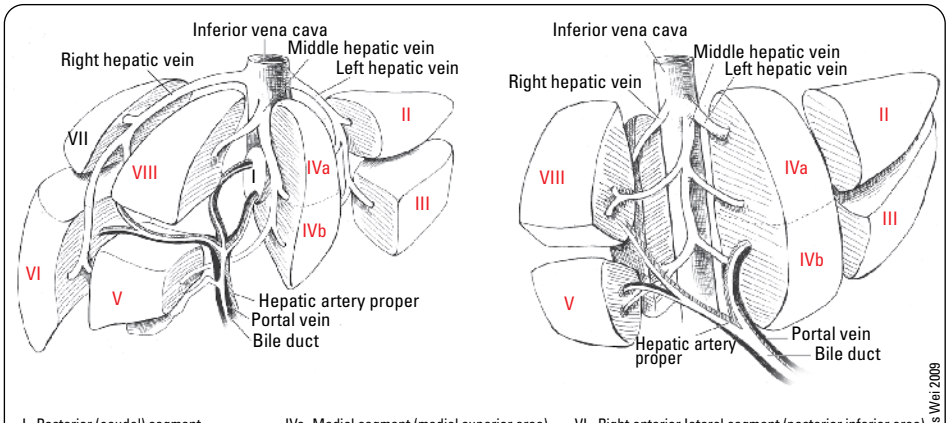
## ANAL CANAL

### Squamous Cell Carcinoma of Anal Canal (Above Dentate Line)
- most common tumour of anal canal (75%)
- anus prone to human papillomavirus (HPV) infection, therefore at risk for anal squamous intra-epithelial lesions (ASIL)
  - high grade squamous intra-epithelial lesion (HSIL) and low grade squamous intra-epithelial lesion (LSIL) terminology used
- clinical features: anal bleeding, pain, mass, ulceration, and pruritus; 25% asymptomatic
- treatment: chemotherapy ± radiation ± surgery
- prognosis: 80% 5-yr survival

### Malignant Melanoma of Anal Canal
- 3rd most common site for primary malignant melanoma after skin, eyes
- aggressive, distant metastases common at time of diagnosis
- treatment: wide excision or abdominal perineal resection (APR) ± chemoradiation
- prognosis: <5% 5 yr survival

## ANAL MARGIN
- clinical features and treatment as for skin tumours elsewhere
- squamous and basal cell carcinoma, Bowen's disease (SCC in situ), and Paget's disease

# Liver




I. Posterior (caudal) segment
II. Lateral segment (lateral superior area)
III. Left anterior lateral segment (lateral inferior area)
IVa. Medial segment (medial superior area)
IVb. Medial segment (medial inferior area)
V. Anterior medial segment (anterior inferior area)
VI. Right anterior lateral segment (posterior inferior area)
VII. Posterior lateral segment (posterior superior area)
VIII. Posterior medial segment (anterior superior area)

**Figure 24. Anatomy of liver**

# Liver Cysts

**Table 24. Characteristics of Liver Cysts**

| | Simple Cysts | Polycystic Liver Disease | Choledochal Cysts | Hydatid (Cystic Echinococcosis) | Cystadenoma (Premalignant)/ Cystadenocarcinoma |
|---|---|---|---|---|---|
| **Description** | Contain clear fluid that do not communicate with the intrahepatic biliary tree<br>Most common<br>May have multiple cysts<br>Always benign | Several cysts that replace much of the liver | Congenital malformations of pancreaticobiliary tree<br>High risk of malignancy<br>Majority present before age 10 | Infection with parasite *Echinococcus granulosus*<br>Associated with exposure to dogs, sheep, and cattle in Southern Europe, Middle East, Australasia, South America | Rare cystic tumours that occur in the liver parenchyma or the extrahepatic bile ducts<br>Cystadenocarcinoma is an invasive carcinoma |
| **Clinical Features** | Usually asymptomatic<br>Dull RUQ pain, bloating, and/or early satiety when symptomatic | Progressive<br>50% associated with polycystic kidney disease (if over age 60) | Recurrent abdominal pain<br>Intermittent jaundice<br>RUQ mass<br>Cholangitis<br>Pancreatitis | Usually asymptomatic<br>May have palpable RUQ mass<br>Chronic RUQ pain when symptomatic | Upper abdominal mass<br>Abdominal pain<br>Anorexia |
| **Investigations** | U/S: Used for diagnosis and follow-up<br>CT: well demarcated lesion that does not enhance with contrast | U/S | U/S<br>CT<br>Transhepatic cholangiography<br>LFTs | Anti-Echinococcus Ab (IgG)<br>U/S<br>CT: calcified mass<br>Needle biopsy | Appear as complex cysts: internal septae, papillary projections, irregular lining<br>Need histology for definite diagnosis |
| **Treatment** | Not required unless very large and/or symptomatic<br>Monitor if >4 cm<br>Laparoscopic or open cyst wall removal (unroofing) is established treatment and is usually curative<br>Percutaneous drainage and ethanol sclerotherapy also an option, but not curative | Only if symptomatic<br>partial liver resection<br>drainage | Complete excision of cysts<br>liver transplant if cyst involves intrahepatic bile ducts (Caroli's disease) | Albendazole (anti-helminthic drug) – cure up to 30%<br>Surgical: radical (total pericystectomy or partial hepatectomy) vs. conservative (open endocystectomy)<br>Percutaneous: PAIR (puncture, aspiration, injection, reaspiration) | All complex, multiloculated cysts (except echinococcal) should be excised because of malignancy risk |
| **Complications** | Intracystic hemorrhage<br>Cyst rupture which can lead to secondary infection | | Biliary cirrhosis, portal HTN, cyst rupture, or cholangiocarcinoma<br>Abnormal pancreaticobiliary junction is associated with increased risk of malignancy | Inferior vena cava compression<br>Cyst rupture which can cause biliary colic, jaundice, cholangitis, pancreatitis, or anaphylactic reaction | Cystadenocarcinoma can invade adjacent tissues and metastasize |

# Liver Abscesses

## Etiology

- types
  - pyogenic (bacterial): most common etiology; most often polymicrobial – *E. coli, Klebsiella, Proteus, Strep. milleri*
  - parasitic (amoebic): *Entamoeba histolytica, Echinococcal* cyst
  - fungal: *Candida*
  - sources: direct spread from biliary tract infection, portal spread from GI infection, systemic infection (e.g. endocarditis)

## Clinical Features

- fever, malaise, chills, anorexia, weight loss, abdominal pain, and nausea
- RUQ tenderness, hepatomegaly, and jaundice

## Investigations

- CBC (leukocytosis, anemia), LFTs (elevated ALP and hypoalbuminemia common; elevated transaminases and bilirubin variable), blood cultures, INR/PTT, stool cultures, and serology (*E. histolytica* and echinoccocus)
- U/S, CXR (right basilar atelectasis/effusion), CT, cyst aspiration with C&S, and MRI

## Treatment

- treat underlying cause
- pyogenic abscesses generally treated with antibiotic therapy (e.g. ceftriaxone and metronidazole or piperacillin-tazobactam) and U/S- or CT-guided percutaneous drainage or surgical drainage
- consider potential source of sepsis (e.g. biliary source, infected tumour)

## Prognosis

- overall mortality 15% – higher rate if delay in diagnosis, multiple abscesses, and malnutrition

# Neoplasms

## BENIGN LIVER NEOPLASMS

### Hemangioma (cavernous)
- pathogenesis: most common benign hepatic tumour; results from malformation of angioblastic fetal tissue
- risk factors: F:M = 3:1
- clinical features
  - usually small and asymptomatic
  - consumptive coagulopathy if giant (in children)
- investigations
  - contrast CT (well-demarcated hypodense mass with peripheral enhancement on arterial phase with centripetal filling on delayed phases), U/S (homogenous hyperechoic mass), MRI
  - avoid biopsy: may result in hemorrhage
- treatment
  - usually none

### Focal Nodular Hyperplasia
- pathogenesis: unclear, may be regenerative response to hyperperfusion from anomalous arteries at centre of nodule
- risk factors: female, age 20-50
- clinical features: asymptomatic, rarely grows or bleeds, and no malignant potential
- investigations: central stellate scar on CT scan; MRI, biopsy may be required
- treatment: may be difficult to distinguish from adenoma/fibrolamellar HCC (malignant potential)
  - if confirmed to be FNH → no treatment required

### Adenoma
- pathogenesis: benign abnormal growth of glandular epithelium
- risk factors: female, age 20-50, estrogen (OCP, pregnancy), obesity, and type 1 glycogen storage disease
- clinical features: asymptomatic, 25% present with RUQ pain or mass, may present with bleeding
- investigations: CT (well-demarcated masses, often heterogeneous enhancement on arterial phase, isodense on venous phase without washout of contrast), U/S, MRI, biopsy can be considered, with bleeding risk taken into account
- treatment
  - stop anabolic steroids or OCP
  - excise, especially if large (>5 cm), due to risk of transformation to HCC and spontaneous rupture/hemorrhage

## MALIGNANT LIVER NEOPLASMS

### Primary
- most commonly hepatocellular carcinoma (HCC) and cholangiocarinomas
- others include angiosarcoma, hepatoblastoma, and hemangioendothelioma
- epidemiology: 4th leading cause of cancer death worldwide, 9th in United States; highest in sub-Saharan Africa and Southeast Asia
- risk factors
  - chronic liver inflammation: cirrhosis from any cause, chronic hepatitis B (inherently oncogenic) and hepatitis C, hemochromatosis, α1-antitrypsin deficiency, and non-alcoholic steatohepatitis
  - medications: OCPs (3x increased risk), steroids
  - smoking, alcohol, betel nuts
  - chemical carcinogens: aflatoxin, microcystin, and vinyl chloride (associated with angiosarcoma)
- clinical features
  - RUQ discomfort and right shoulder pain
  - jaundice, weakness, weight loss, and ± fever (if central tumour necrosis)
  - hepatomegaly, bruit, and hepatic friction rub
  - ascites with blood (sudden intra-abdominal hemorrhage)
  - paraneoplastic syndromes: hypoglycemia, hypercalcemia, erythrocytosis, and watery diarrhea
  - metastasis: lung, bone, brain, and peritoneal seeding
- investigations
  - elevated ALP, bilirubin, and α-fetoprotein (80% of patients)
  - U/S (poorly-defined margins with internal echos), triphasic CT (enhancement on arterial phase and washout on portal venous phase), and MRI
  - liver enzyme and liver function tests: AST, ALT, ALP, bilirubin, albumin, and INR
- treatment
  - cirrhosis is a relative contraindication to tumour resection due to decreased hepatic reserve
  - surgical: resection (10% of patients have resectable tumours)
  - liver transplant; may use bridging therapy while awaiting transplant
    - absolute contraindications: extrahepatic disease and vascular invasion
    - relative contraindications: dependent on liver transplant protocol based on staging criteria followed by transplant centre
  - non-surgical: radiofrequency ablation, percutaneous ethanol injection, transcatheter arterial chemoembolization (TACE), chemotherapy (consider sorafenib for HCC; pre-operative chemotherapy for hepatoblastoma is standard of care), and radiotherapy

**Differential Diagnosis of Metastatic Liver Mass**

**S**ome **GU** **C**ancers **P**roduce **B**umpy **L**umps
**S**tomach
**G**enito**U**rinary cancers (kidney, ovary, uterus)
**C**olon
**P**ancreas
**B**reast
**L**ung

**Staging Criteria for Hepatocellular Carcinoma**

| | |
|---|---|
| **Milan Criteria*** | 1 tumour ≤5 cm<br>Up to 3 tumours each ≤3 cm |
| **UCSF Criteria*** | 1 tumour ≤6.5 cm<br>Up to 3 tumours each ≤4.5 cm, total diameter ≤8 cm |
| **Toronto Criteria*** | No tumour size or number restrictions<br>No systemic symptoms<br>Not poorly differentiated |

*Each criteria assumes no extrahepatic and no macrovascular invasion

**Child-Turcotte-Pugh Score (Prognosis of Chronic Liver Disease/Cirrhosis, including Post-Operatively)**

| | 1 Point | 2 Points | 3 Points |
|---|---|---|---|
| **Albumin (g/L)** | >35 | 28-35 | <28 |
| **Ascites** | Absent | Easily controlled | Poorly controlled |
| **Bilirubin (μmol/L)** | <34 | 34-51 | >51 |
| **(mg/dL)** | <2.0 | 2.0-3.0 | >3.0 |
| **Coagulation (INR)** | <1.7 | 1.7-2.3 | >2.3 |
| **Hepatic Encephalopathy** | None | Minimal (Grade I-II) | Advanced (Grade III-IV) |

| Points | Class | One Yr Survival | Two Yr Survival |
|---|---|---|---|
| **5-6** | A | 100% | 85% |
| **7-9** | B | 81% | 57% |
| **10-15** | C | 45% | 35% |

- prognosis
  - 5 yr survival: 18% of all patients; 40-70% of patients undergoing complete resection

### Secondary
- metastases to the liver are the most common malignant tumours found in the liver
- etiology
  - GI (colorectal most common), lung, breast, pancreas, ovary, uterus, kidney, gallbladder, and prostate
- treatment
  - depends on the primary cancer site and prognosis
    - often liver metastases are a manifestation of Stage IV disease and chemotherapy is indicated
  - metastasectomy may be appropriate for some cancers
    - hepatic resection of metastatic colorectal liver metastases is standard of care as part of multi-modality treatment that includes chemotherapy if complete resection of the primary cancer and metastases is possible
    - prognosis following liver resection for colorectal metastases is an overall survival of 30-60% at 5 yr

Secondary liver metastases are common in many cancers, with some studies showing a prevalence of 40-50% amongst patients with extrahepatic cancers. They commonly arise from breast, lung, and colorectal cancers. For metastases secondary to colorectal cancer, surgical resection offers the greatest likelihood of cure

## Liver Transplantation

**Table 25. Conditions Leading to Transplantation**

| Parenchymal Disease | Cholestatic Disease | Inborn Errors | Tumours |
|---|---|---|---|
| Chronic hepatitis B or C*<br>Alcoholic cirrhosis<br>Acute liver failure<br>Budd-Chiari syndrome<br>Congenital hepatic fibrosis<br>CF<br>Autoimmune hepatitis<br>Cryptogenic cirrhosis<br>Drug induced hepatotoxicity<br>Non-alcoholic steatohepatitis | Biliary atresia**<br>Primary biliary cirrhosis<br>Sclerosing cholangitis | α1-antitrypsin deficiency<br>Wilson's disease<br>Hemochromatosis | Hepatocellular carcinoma |

*leading cause in adults; **leading cause in children

**Living Liver Donors vs. Deceased Liver Donors**
The right lobe of a living donor liver is transplanted into the recipient, whereas whole livers from deceased donors are transplanted orthotopically into the recipient

### Clinical Indications
- early referral for transplant should be considered for all patients with progressive liver disease not responsive to medical therapy, especially:
  - decompensated cirrhosis (ascites, esophageal variceal hemorrhage, spontaneous hepatic encephalopathy, coagulopathy, progressive jaundice, severe fatigue)
  - unresectable primary liver cancers
  - fulminant hepatic failure
- end-stage liver disease with life expectancy <1 yr and if no other therapy is appropriate
  - suitable HCC not amenable to liver resection

**Which Matters Most: Number of Tumours, Size of the Largest Tumour, or Total Tumour Volume?**
Liver Transplant 2011;17:S58-66
**Purpose**: To determine if the size and/or number of hepatocellular carcinoma (HCC) nodules predict disease recurrence and survival after liver transplantation.
**Methods**: Systematic review and meta-analysis.
**Results**: 74 studies were included for analysis. Patients beyond the Milan criteria had reduced overall and disease-free survivals and higher recurrence. Patients outside the UCSF criteria had reduced overall and disease-free survivals and higher recurrence. Patients outside the Milan criteria but within the UCSF criteria had reduced overall and disease-free survivals. Overall and disease-free survivals were reduced for patients with larger total tumour diameter, ≥10 cm vs. <10 cm and ≥9 cm vs. <9 cm, respectively. Similarly, patients with higher diameter of largest tumour nodule (≥3 cm vs. <3 cm) had reduced overall survival and higher recurrence. Overall and disease-free survivals were reduced and recurrence higher for patients with tumour size ≥5 cm vs. <5 cm. Mixed results were found regarding number of tumour nodules.
**Conclusion**: Tumour size and volume are important factors in survival after liver transplantation.

### Criteria for Transplantation
- Model for End-Stage Liver Disease (MELD): prognostic model to estimate 3 mo survival following transjugular intrahepatic portosystemic shunt (TIPS) procedure and to prioritize patients awaiting liver transplant; based on creatinine, bilirubin, INR; MELD scores from 6-40 used to prioritize liver allocation
- Child-Turcotte-Pugh Score: classification system to assess the prognosis and the abdominal surgery peri-operative mortality of chronic liver disease and cirrhosis; patient must have ≥7 points (Class B) for transplant evaluation

### Contraindications
- active alcohol/substance abuse
- extrahepatic malignancy within 5 yr
- advanced cardiopulmonary disease
- active uncontrolled infection

**Living Donor Liver Transplantation vs. Deceased Donor Liver Transplantation for Hepatocellular Carcinoma: Comparable Survival and Recurrence**
Liver Transplant 2012;18:315-322
**Purpose**: To compare the overall survival and hepatocellular carcinoma (HCC) recurrence rates after living donor liver transplantation (LDLT) versus deceased donor liver transplantation (DDLT) in a series of patients with HCC.
**Methods**: Study conducted between 1996 and 2009 at a single centre. 345 patients with HCC undergoing liver transplantation included.
**Results**: The overall survival rates at 1, 3, and 5 yr did not significantly differ between the LDLT and DDLT groups (p=0.62). Disease free survival at 1, 3, and 5 yr did not differ between the groups (p=0.82). The recurrence rates at 1, 3, and 5 yr also did not differ between the two group (p=0.54).
**Conclusion**: LDLT and DDLT lead to similar survival and recurrence rates.

### Post-Operative Complications
- primary non-function (graft failure): urgent re-transplantation is indicated
- acute and chronic rejection, ischemia-reperfusion injury
- vascular: hepatic artery or portal vein thrombosis, IVC obstruction
- biliary complications: fever, increasing bilirubin and ALP
- complications related to immunosuppression: HTN, renal disease, DM, obesity, hyperlipidemia, osteoporosis, malignancy, neurologic complications, infection (leading cause of mortality following transplant)

### Prognosis
- patient survival at 1 yr: 85%
- graft survival at 1 yr: >80%, at 5 yr: 60-70%

# Biliary Tract

## Cholelithiasis

### Definition
- the presence of stones in the gallbladder

### Pathogenesis
- imbalance of cholesterol and its solubilizing agents (bile salts and lecithin)
- excess hepatic cholesterol secretion relative to bile salts and lecithin → supersaturated cholesterol which precipitates as gallstones
- North America: cholesterol stones (80%), pigment stones (20%)

### Risk Factors
- cholesterol stones
  - obesity
  - age <50
  - estrogens: female, multiparity, OCPs
  - ethnicity: First Nations heritage (especially Pima Indians) > Caucasian > Black
  - terminal ileal resection or disease (e.g. Crohn's disease)
  - impaired gallbladder emptying: starvation, TPN, DM
  - rapid weight loss: rapid cholesterol mobilization and biliary stasis
- pigment stones (contain calcium bilirubinate)
  - cirrhosis
  - chronic hemolysis
  - biliary stasis (strictures, dilation, biliary infection)
  - protective factors: statins, vitamin C, coffee, exercise

**Risk Factors for Cholesterol Stones**

**4Fs**
**F**at
**F**emale
**F**ertile
**F**orties

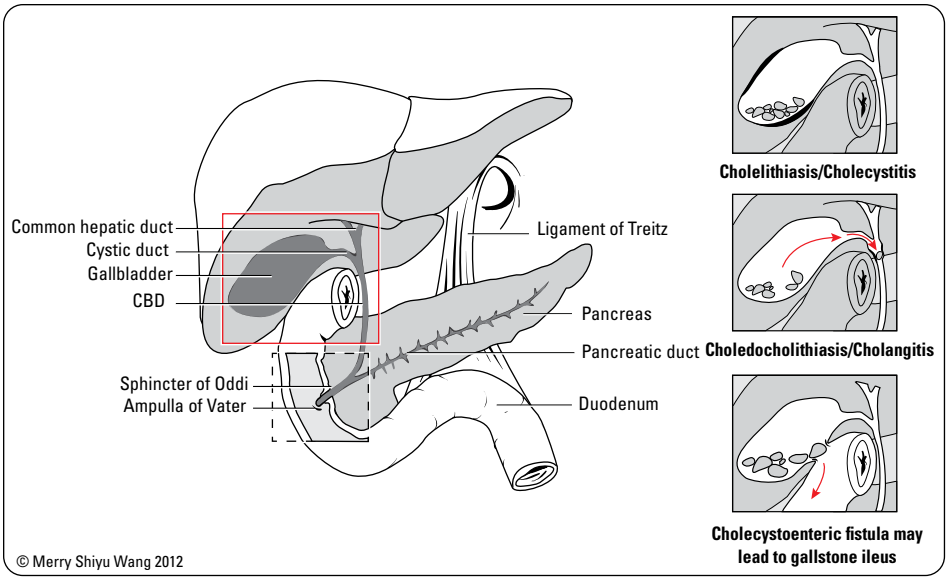



**Figure 25. Gallstone disease**

### Clinical Feature
- asymptomatic (80%): found incidentally
  - 18% risk of progression to symptomatic gallstone disease within 20 yr
  - most do NOT require treatment
  - consider cholecystectomy if: increased risk of malignancy (choledochal cysts, Caroli's disease, porcelain or calcified gallbladder), sickle cell disease, pediatric patient, bariatric surgery, and immunosuppression
- biliary colic (10-25%)

### Investigations
- normal bloodwork: CBC, LFTs, liver enzymes, amylase, lipase
- U/S: diagnostic procedure of choice
  - image for signs of inflammation, obstruction, and localization of stones
  - 95% specific for detecting stones
- HIDA scan (cholescintography)
  - used less commonly
  - IV technetium-99 radioisotope is excreted into bile, allowing visualization of the biliary tree
  - does not visualize stones; diagnosis based on occluded cystic duct or CBD

**Summary of Biliary Tract Conditions**

| Gall Bladder | Asymptomatic | Pain Only | Infection + Pain |
|---|---|---|---|
| Cholelithiasis | ✓ (majority) | | |
| Biliary Colic | | ✓ | |
| Cholecystitis | | | ✓ |
| **Common Bile Duct** | **Asymptomatic** | **Pain Only** | **Infection + Pain** |
| Choledocholithiasis | ✓ (majority) | ✓ | |
| Cholangitis | | | ✓ (majority) |

# Biliary Colic

### Pathogenesis
- gallstone transiently impacted in cystic duct, no infection

### Clinical Features
- an episode of steady, severe dull pain in the epigastrium or RUQ lasting minutes to hours (<6 h), crescendo-decrescendo pattern
- can present with chest pain, right shoulder tip pain, scapular pain
- N/V
- frequently occurs at night or after fatty meal, not after fasting
- no peritoneal findings, no systemic signs

### Investigations
- normal blood work: CBC, electrolytes, liver enzymes, LFTs, bilirubin, amylase
- U/S shows cholelithiasis, may show stone in cystic duct

### Treatment
- analgesia, rehydration during colic episode
- elective cholecystectomy (95% success)
  - complications: CBD injury (0.3-0.5%), hollow viscus injury, bile peritonitis, and vessel injury
  - laparoscopic cholecystectomy is the standard of care, no benefit to delaying surgery
  - risk of open cholecystectomy higher in emergency situations

# Acute Cholecystitis

### Pathogenesis
- inflammation of gallbladder resulting from sustained gallstone impaction in cystic duct or Hartmann's pouch
- no cholelithiasis in 5-10% (see *Acalculous Cholecystitis*, GS53)

### Clinical Features
- often have history of biliary colic
- severe constant (>6 h) epigastric or RUQ pain, anorexia, N/V, and low grade fever (<38.5°C)
- focal peritoneal findings: Murphy's sign, palpable, and tender gallbladder (in 33%)
- Boas' sign: right subscapular pain

### Investigations
- blood work: elevated WBC and left shift, mildly elevated bilirubin, AST, ALT, and ALP
- U/S: 98% sensitive, consider HIDA scan if U/S negative
  - signs: gallbladder wall thickening >4 mm, edema (double-wall sign), gallbladder sludge, pericholecystic fluid, and sonographic Murphy's sign

### Complications
- Mirizzi syndrome: extra-luminal compression of CBD/CHD due to large stone in cystic duct
- empyema of gallbladder: suppurative cholecystitis, pus in gallbladder, and sick patient
- emphysematous cholecystitis: bacterial gas present in gallbladder lumen, wall, or pericholecystic space (risk in diabetic patient); organisms involved in secondary infection: *E. coli, Klebsiella, Enterococcus*
- gangrenous gallbladder (20%), perforation (2%): result in abscess formation or peritonitis
- cholecystoenteric fistula (from repeated attacks of cholecystitis) can lead to gallstone ileus

### Treatment
- admit, hydrate, NPO, NGT (if persistent vomiting from associated ileus), analgesics
- antibiotics
  - cefazolin if uncomplicated cholecystitis
- ERCP prior to surgery if CBD stones are present on US
  - MRCP ± ERCP if CBD is markedly dilated or CBD stones suspected
- cholecystectomy
  - early (within 72 h) vs. delayed (after 6 wk)
    - equal morbidity and mortality
    - early cholecystectomy preferred: shorter hospitalization and recovery time, no benefit to delaying surgery
    - emergent OR indicated if high risk, e.g. emphysematous
  - laparoscopic is standard of care (convert to open for complications or difficult case)
    - laparoscopic: reduced risk of wound infections, shorter hospital stay, reduced post-operative pain, and increased risk of bile duct injury
- intra-operative cholangiography (IOC)
  - indications: clarify bile duct anatomy, history of biliary pancreatitis, small stones in gallbladder with a wide cystic duct (>15 mm), and jaundice
- percutaneous cholecystostomy tube: critically ill or if general anesthetic contraindicated



Biliary colic is a **constant pain**, not colicky



**2 Most Important Lab Tests for Biliary Pain**
- Lipase
- Bilirubin



Biliary colic is treated with analgesia and elective cholecystectomy
Acute cholecystitis is treated with antibiotics and early cholecystectomy



**Early vs. Delayed Laparoscopic Cholecystectomy for Uncomplicated Biliary Colic**
Cochrane DB Syst Rev 2013;6:CD007196
**Study**: To assess the benefits and harms of early vs. delayed laparoscopic cholecystectomy for patients with uncomplicated biliary colic due to gallstones.
**Results**: One trial with 75 participants, average age 43 yr. Early laparoscopic cholecystectomy (<24 h) vs. delayed (mean wait period 4.2 mo). The proportion of serious adverse events was lower in the early vs. delayed group (0% vs. 22.5%, respectively). There was a shorter hospital stay in the early group (MD -1.25 d, 95% CI -2.05 to -0.45) and a shorter operating time in the early group (MD -14.80 min, 95% CI -18.02 to -11.58). There was no difference in the proportion of patients requiring conversion to open cholecystectomy in the two groups.
**Conclusion**: Early laparoscopic cholecystectomy (<24 h of diagnosis of biliary colic) decreased morbidity during the waiting period for elective laparoscopic cholecystectomy, hospital stay, and operating time.

# Acalculous Cholecystitis

## Definition
- acute or chronic cholecystitis in the absence of stones

## Pathogenesis
- typically due to gallbladder ischemia and stasis

## Risk Factors
- DM, immunosuppression, ICU admission, trauma patient, TPN, and sepsis

## Clinical Features
- see *Acute Cholecystitis*, GS52
- occurs in 10% of cases of acute cholecystitis

## Investigations
- bloodwork: CBC, electrolytes, LFTs, liver enzymes, amylase, and lipase
- U/S: shows sludge in gallbladder, other U/S features of cholecystitis (see *Acute Cholecystitis*, GS52)
- CT or HIDA scan

## Treatment
- IV fluids, pain management
- broad-spectrum antibiotics, cholecystectomy
- if patient unstable → cholecystostomy

# Choledocholithiasis

## Definition
- stones in CBD

## Clinical Features
- 50% asymptomatic
- often have history of biliary colic
- tenderness in RUQ or epigastrium
- acholic stool, dark urine, and fluctuating jaundice
- primary vs. secondary stones
  - primary: formed in bile duct, indicates bile duct pathology (e.g. benign biliary stricture, sclerosing cholangitis, choledochal cyst, and CF)
  - secondary: formed in gallbladder (85% of cases in U.S.)

## Investigations
- CBC: usually normal; leukocytosis suggests cholangitis
- LFTs: increased AST, ALT early in disease, increased bilirubin (more sensitive), alkaline phosphatase (ALP), gamma glutamyltransferase (GGT) later
- amylase/lipase: to rule out gallstone pancreatitis
- U/S: intra-/extra-hepatic duct dilatation; differential diagnosis is choledochal cyst
- MRCP (90% sensitive)
  - visualization of ampullary region, biliary and pancreatic anatomy
  - non-invasive diagnostic test of choice
- ERCP
  - CBD stones in periampullary region
  - diagnostic and therapeutic; removal of stones and sphincterotomy possible
  - complications: retained stones, ERCP pancreatitis (1-2%), pancreatic or biliary sepsis

## Percutaneous Transhepatic Cholangiography
- percutaneous approach to the proximal biliary tree (i.e. intra-hepatic biliary system) via the hepatic parenchyma
- useful for proximal bile duct obstruction or when ERCP fails or not available
- requires prophylactic antibiotics
- contraindications: coagulopathy, ascites, peri/intrahepatic sepsis, and disease of right lower lung or pleura
- complications: bile peritonitis, chylothorax, pneumothorax, biliary sepsis, and hemobilia

## Complications
- cholangitis, pancreatitis, biliary stricture, and biliary cirrhosis

## Treatment
- treat with ERCP for CBD stone extraction possibly followed by elective cholecystectomy in 25% of patients



**Mirizzi Syndrome**
Extrinsic compression of the common hepatic duct by a gallstone in the cystic duct or Hartmann's pouch. Impacted gallstone may erode into the CHD or CBD, creating a cholecystohepatic or cholecystocholedochal fistula; Mirizzi syndrome has an association with gallbladder cancer



**Rouviere's Sulcus**
Fissure between right lobe and caudate process of liver; keeping dissection anterior to this landmark prevents bile duct injury



**Critical View of Safety**
Decreases risk of injury to CBD during laparoscopic cholecystectomy
Hepatocystic triangle (space between the gallbladder and liver) cleared of any structures other than the cystic artery



**Laparoscopic vs. Open Cholecystectomy**
**Laparoscopic Cholecystectomy**
- Shorter operating time
- Shorter length of stay
- Shorter sick leave
- Shorter time to return to daily activities
- Less post-operative pain
- Decreased use of post-operative analgesia
- Decreased reduction in pulmonary function*
- Fewer pulmonary complications
- Decreased acute phase response
- Less impairment in intestinal motility*

**Open Cholecystectomy**
- Lower conversion rates to open surgery (for mini-laparotomies)

*NOTE:
Pulmonary function = $O_2$ consumption, spirometric parameters, ABG, and acid-base balance
Intestinal motility = auscultating intestinal peristalsis, abdominal circumference measurement, and time interval to restitution of defecation



**American Society of Gastrointestinal Endoscopy 2010 Predictors for Risk of CBD Stones**
**Very strong**
- CBD stone on U/S
- Clinical ascending cholangitis
- Bilirubin >68 µmol/L

**Strong**
- CBD dilated >6 mm on U/S
- Bilirubin 31-68 µmol/L

**Moderate**
- Abnormal liver test (besides bilirubin)
- Age >55 yr
- Clinical gallstone pancreatitis

# Acute Cholangitis

### Pathogenesis
- obstruction of CBD leading to biliary stasis, bacterial overgrowth, suppuration, and biliary sepsis – may be life-threatening, especially in elderly

### Etiology
- choledocholithiasis (60%), stricture, neoplasm (pancreatic or biliary), extrinsic compression (pancreatic pseudocyst or pancreatitis), instrumentation of bile ducts (PTC, ERCP), and biliary stent
- organisms: *E. coli, Klebsiella, Pseudomonas, Enterococcus, B. fragilis, and Proteus*

### Clinical Features
- Charcot's triad: fever, RUQ pain, and jaundice
- Reynold's pentad: fever, RUQ pain, jaundice, shock, and confusion
- may have N/V, abdominal distention, ileus, acholic stools, and tea-coloured urine (elevated direct bilirubin)

### Investigations
- CBC: elevated WBC + left shift
- may have positive blood cultures
- LFTs: obstructive picture (elevated ALP, GGT, and conjugated bilirubin, mild increase in AST, ALT)
- amylase/lipase: rule out pancreatitis
- U/S: intra-/extra-hepatic duct dilatation

### Treatment
- initial: NPO, fluid and electrolyte resuscitation, ± NGT, IV antibiotics (treats 80%)
- biliary decompression
  - ERCP + sphincterotomy: diagnostic and therapeutic
  - PTC with catheter drainage: if ERCP not available or unsuccessful
  - laparotomy with CBD exploration and T-tube placement if above fails
- all patients should also have a cholecystectomy, unless contraindicated

### Prognosis
- suppurative cholangitis mortality rate: 20-30%

**Charcot's Triad**
Fever, RUQ pain, jaundice

**Reynolds' Pentad**
Fever, RUQ pain, jaundice, shock, confusion

**Common Bacteria in Biliary Tract**

**KEEPS**
***K****lebsiella*
***E****nterococcus*
***E****. coli,* ***E****nterobacter*
***P****roteus,* ***P****seudomonas*
***S****erratia*

# Gallstone Ileus

### Pathogenesis
- repeated inflammation causes a cholecystoenteric fistula (usually duodenal) → large gallstone enters the GI tract (impacting near the ileocecal valve) causing a mechanical bowel obstruction (note: ileus is a misnomer in this context)

### Clinical Features
- crampy abdominal pain, N/V, constipation/obstipation (see *Large Bowel Obstruction*, GS34)

### Investigations
- AXR: dilated small intestine, air fluid levels, may reveal radiopaque gallstone, and air in biliary tree (pneumobilia) (40%)
- CT: biliary tract air, obstruction, and gallstone in intestine
- Rigler's triad: pneumobilia, small bowel obstruction (partial or complete), and gallstone (usually in right iliac fossa)

### Treatment
- fluid resuscitation, NGT decompression
- surgery: enterolithotomy and removal of stone, inspect small and large bowel for additional proximal stones
- may close fistula surgically or manage expectantly (can resolve spontaneously)
- cholecystectomy is generally not performed

**Rigler's Triad of Gallstone Ileus**
Pneumobilia
Small bowel obstruction
Gallstone

**Bouveret's Syndrome**
Gastric outlet/duodenal obstruction caused by a large gallstone passing through a cholecystogastric or cholecystoduodenal fistula

# Carcinoma of the Gallbladder

### Risk Factors
- chronic symptomatic gallstones (70% of cases), old age, female, gallbladder polyps, porcelain gallbladder, chronic infection (*Salmonella, Helicobacter*), and abnormal pancreaticobiliary duct junction

### Clinical Features
- majority are adenocarcinoma
- may be incidental finding on elective cholecystectomy (~1% of open cholecystectomies OR 0.1% in laparoscopic cholecystectomies)
- many patients are asymptomatic until late
- local: non-specific RUQ pain, ± palpable RUQ mass
- Courvoisier's gallbladder sign: enlarged gallbladder and painless jaundice due to obstruction of CBD, suggestive of gallbladder or pancreatitic malignancy
- systemic: jaundice (50%) due to invasion of CBD or compression of CBD by pericholedochal nodes, weight loss, malaise, anorexia
- early local extension to liver, may extend to stomach, duodenum
- early metastasis common to liver, lung, bone

### Investigations
- U/S: mural thickening, calcification, loss of interface between gallbladder and liver, and fixed mass
- endoscopic U/S (EUS): good for distinguishing carcinomas from other diagnoses such as polyps, staging, allows sampling of bile for cytology
- abdominal CT: polypoid mass, mural thickening, liver invasion, nodal involvement, and distant metastases
- MRI/MRCP: good for distinguishing benign and malignant polyps

### Treatment
- if carcinoma of the gallbladder is suspected pre-operatively, an open cholecystectomy should be considered to avoid tumour seeding of the peritoneal cavity
- confined to mucosa (rare): cholecystectomy
- beyond mucosa: cholecystectomy, en bloc wedge resection of 3-5 cm underlying liver, and dissection of hepatoduodenal lymph nodes

### Prognosis
- poor 5 yr survival (20%) as gallbladder carcinoma is often detected late
- better outcomes when detected incidentally following cholecystectomy

**Efficacy of Neoadjuvant Chemoradiation, Followed by Liver Transplantation, for Perihilar Cholangiocarcinoma at 12 US Centres**
Gastroenterology 2012;143:88-98
**Purpose**: To determine the effectiveness of neoadjuvant chemoradiation and liver transplantation for unresectable perihilar cholangiocarcinoma and to determine the appropriateness of the United Network of Organ Sharing/ Organ Procurement and Transplantation Network (UNOS/ OPTN) criteria for model of end-stage liver disease (MELD) exception for patients with this disease.
**Methods**: Study conducted from 1993-2010 in 12 transplant centres. 287 patients included.
**Results**: Median follow-up was 2.5 yr. 43% of patients (n=122) died after a median of 1.2 yr from presentation, and of these, 60 died pretransplant. Post-transplant, 43 patients had recurrences and 62 died. Recurrence-free survival at 2, 5, and 10 yr were 78%, 65%, and 59%, respectively. Intention-to-treat survival rates at 2 and 5 yr were 68% and 53%, respectively. 25% of patients left the waiting list after a median of 4.6 mo. The waiting list drop-out rate increased by an average of 11.5% every 3 mo. Patients who received transplantation outside of the criteria for MELD exception or who had a malignancy within 5 yr had significantly worse recurrence-free survival compared to those who met the criteria (HR=2.98, 95% CI 1.79, 4.95). Recurrence-free survival at 5 yr was shorter for patients with tumours >3 cm vs. ≤3 cm ($p<0.001$).
**Conclusions**: Neoadjuvant chemoradiation and liver transplantation are effective treatments for unresectable perihilar cholangiocarcinoma. Furthermore, the UNOS/ OPTN criteria for MELD exception appear to be appropriate.

Obstructive jaundice is the most common presenting symptom for cholangiocarcinoma

# Cholangiocarcinoma

### Definition
- malignancy of extra- or intrahepatic bile ducts

### Risk Factors
- age 50-70, gallstones, ulcerative colitis, primary sclerosing cholangitis, choledochal cyst, *Clonorchis sinensis* infection (liver fluke), chronic intrahepatic stones (hepatolithiasis)

### Clinical Features
- majority are adenocarcinomas
- gradual signs of biliary obstruction: jaundice, pruritus, dark urine, and pale stools
- anorexia, weight loss, RUQ pain, Courvoisier's sign (if CBD obstructed), hepatomegaly
- early metastases are uncommon, but commonly tumour grows into portal vein or hepatic artery
- Klatskin tumour: cholangiocarcinoma located at bifurcation of common hepatic duct

### Investigations
- LFTs show obstructive picture
- U/S, CT: bile ducts usually dilated, but not necessarily
- ERCP or PTC: to determine resectability, for biopsies
- CXR, bone scan: for metastatic workup

### Treatment
- if resectable: biliary drainage and wide excision margin
- intra-hepatic lesions: liver resection
  - upper third lesions: duct resection + Roux-en-Y hepaticojejunostomy, ± liver resection
  - middle third lesions (uncommon): duct resection + Roux-en-Y hepaticojejunostomy
  - lower third lesions: Whipple procedure
- unresectable lesions: stent or choledochojejunostomy (surgical bypass)
- chemotherapy ± radiotherapy
- role for transplantation in selected patients with Klatskin tumours

### Prognosis
- overall 5 yr survival: localized 30%, regional 24%, distant 2%

# Pancreas

## Acute Pancreatitis

- see Gastroenterology, G46

### GALLSTONE PANCREATITIS (45% of Acute Pancreatitis)

#### Pathogenesis
- obstruction of pancreatic duct by large or small gallstones and biliary sludge
- backup of pancreatic enzymes can cause autodigestion of the pancreas

#### Clinical Features (Pancreatitis of Any Etiology)
- pain (epigastric pain radiating to back), N/V, ileus, peritoneal signs, jaundice, and fever
- Inglefinger's sign: pain worse when supine, and better when sitting forward
- may have coexistent cholangitis or pancreatic necrosis
- Ranson's criteria for determining prognosis of acute pancreatitis (see sidebar)
  - APACHE II score for determining prognosis of severe acute pancreatitis
- physical exam may show: tachypnea, tachycardia, hypotension, abdominal distention and tenderness, Cullen's sign, and Grey Turner's sign

#### Investigations
- lipase (most Sn and Sp), elevated amylase (higher than alcoholic pancreatitis), and leukocytosis
- elevated ALT (>150 IU/L), AST strongly suggest gallstone etiology of pancreatitis
- U/S may show multiple stones (may have passed spontaneously), and edematous pancreas
- CXR, AXR, and CT (if severe to evaluate for complications)

#### Treatment
- supportive: e.g. NPO, hydration, analgesia, and early enteric nutrition
- antibiotics for severe cases of necrotizing pancreatitis or signs of sepsis
- stone often passes spontaneously (~90%); usually no surgical management in uncomplicated acute pancreatitis
- cholecystectomy during same admission (25-60% recurrence if no surgery)
- may need urgent ERCP + sphincterotomy if CBD stone impacted or cholangitis
- surgical indications in acute pancreatitis (rare):
  - drain placement and debridement for necrotizing pancreatitis if refractory to medical management, if septic, or in ICU without other sources of sepsis

#### Complications
- local complications
  - acute fluid collections
  - walled-off pancreatic fluid collection/pseudocyst (>4 wk old)
  - abscess/infection, necrosis
- systemic complications
  - splenic/mesenteric/portal vessel thrombosis
  - pancreatic ascites/pancreatic pleural effusion
  - DM (b/c pancreatic & insulin insufficiency)
  - ARDS/sepsis/multiorgan failure
  - coagulopathy/DIC
  - severe hypocalcemia

**Ranson's Criteria**
**A. At admission**
1. Age >55 yr
2. WBC >16 x $10^9$/L
3. Glucose >11 mmol/L
4. LDH ≥350 IU/L
5. AST >250 IU/L

**B. During initial 48 h**
1. Hct drop >10%
2. BUN rise >1.8 mmol/L
3. Arterial $PO_2$ <60 mmHg
4. Base deficit >4 mmol/L
5. Calcium <2 mmol/L
6. Fluid sequestration >6 L

**C. Interpretation**
≥2 = difficult course
≥3 = high mortality (≥15%)

## Chronic Pancreatitis

- see Gastroenterology, G48

The hallmark of chronic pancreatitis is epigastric pain radiating to the back

#### Surgical Treatment
- treatment is generally medical
- indications for surgery
  - failure of medical treatment
  - debilitating abdominal pain
  - pseudocyst complications: persistence, hemorrhage, infection, and rupture
  - CBD obstruction (e.g. strictures), and duodenal obstruction
  - pancreatic fistula, variceal hemorrhage secondary to splenic vein obstruction
  - rule out pancreatic cancer (present in 15% of chronic pancreatitis treated surgically)
  - anatomical abnormality causing recurrent pancreatitis
- pre-operative CT and/or ERCP are mandatory to delineate anatomy
- minimally invasive options
  - endoscopic pancreatic duct decompression: less effective than surgery
  - extracorporeal shockwave lithotripsy: if pancreatic duct stones
  - celiac plexus block: lasting benefit in 30% patients, less effective in those <45 yr or with prior pancreatic surgery

- surgical options
  - drainage procedures: only effective if ductal system is dilated
  - Puestow procedure (lateral pancreaticojejunostomy): improves pain in 80% of patients
  - pancreatectomy: best option in absence of dilated duct
  - Whipple procedure (pancreaticoduodenectomy): proximal disease
  - distal pancreatectomy ± Roux-en-Y pancreaticojejunostomy: distal disease
  - total pancreatectomy: refractory disease
- islet cells autotransplantation can be used to control insulin-related morbidity
  - denervation of celiac ganglion and splanchnic nerves

### WALLED-OFF PANCREATIC FLUID COLLECTIONS (PSEUDOCYST)

- localized fluid collections rich in pancreatic enzymes, with a non-epithelialized wall consisting of fibrous and granulation tissue
- complication of chronic and/or acute pancreatitis
- up to 40% resolve spontaneously
- cyst wall must be mature prior to drainage (4-6 wk)
- pseudoaneurysm an absolute contraindication to endoscopic drainage, must embolize first

#### Treatment

- if asymptomatic: expectant management
- if symptomatic: choice of drainage procedure depends on location of fluid collection
  - endoscopic drainage: transmural vs. transpapillary
  - surgical drainage: cystogastrostomy vs. cystoduodenostomy vs. cystojejunostomy
  - percutaneous catheter drainage
  - resection
  - consider biopsy of cyst wall to rule out cystadenocarcinoma

**Total Pancreatectomy and Islet Autotransplantation: A Decade Nationwide Analysis**
World J Transplant 2016;6(1):233-38
**Aim**: To investigate outcomes and predictors of in-hospital morbidity and mortality after total pancreatectomy (TP) and islet autotransplantation.
**Results**: We evaluated a total of 923 patients who underwent IAT after pancreatectomy during 2002-2012. The most common indication of surgery was chronic pancreatitis (86%) followed by acute pancreatitis (12%). Overall mortality and morbidity of patients were 0% and 57.8 %, respectively. Post-surgical hypoinsulinemia was reported in 42.3% of patients, indicating that 57.7% of patients were insulin independent during hospitalization. Predictors of in-hospital morbidity were obesity, fluid and electrolyte disorders, alcohol abuse, and weight loss.
**Conclusion**: Total pancreatectomy + islet autotransplantation is a safe procedure with no mortality, acceptable morbidity, and achieved high rate of early insulin independence. Obesity is the most significant predictor of in-hospital morbidity.

## Pancreatic Cancer

### Epidemiology

- fourth most common cause of cancer-related mortality in both men and women in Canada
- M:F = 1.3:1, average age: 50-70 yr

### Risk Factors

- increased age
- smoking: 2-5x increased risk, most clearly established risk factor
- high fat/low fibre diets
- heavy alcohol use
- obesity
- DM, chronic pancreatitis
- partial gastrectomy
- cholecystectomy
- chemicals: β-naphthylamine, benzidine
- African descent

**Trousseau's Sign**
Spontaneous peripheral venous thrombosis, often associated with pancreatic and other cancers

Vague abdominal pain with weight loss ± jaundice in a patient over 50 yr is pancreatic cancer until proven otherwise

### Clinical Features

- head of the pancreas (70%)
  - weight loss, obstructive jaundice, steatorrhea, and vague constant mid-epigastric pain (often worse at night, may radiate to back)
  - painless jaundice, pruritis, dark urine, pale stools, and Courvoisier's sign
- body or tail of pancreas (30%)
  - tends to present later and usually inoperable (80% are unresectable at diagnosis)
  - weight loss, vague mid-epigastric pain
  - <10% jaundiced
  - sudden onset DM

**Courvoisier's Sign**
Palpable, nontender, distended gallbladder due to CBD obstruction. Present in 33% of patients with pancreatic carcinoma. The distended gallbladder could not be due to acute cholecystitis or stone disease because the gallbladder would actually be scarred and smaller, not larger

### Investigations

- serum chemistry is non-specific, can have elevated ALP and high bilirubin
- carbohydrate antigen 19-9 (most useful serum marker of pancreatic cancer)
- U/S, CT (also evaluates metastasis and resectability) ± ERCP, MRI, EUS

### Pathology

- ductal adenocarcinoma: most common type (75-80%); exocrine pancreas
- intraductal papillary mucinous neoplasm (IPMN)
- other: pancreatic neuroendocrine tumours (non-functional, insulinoma, gastrinoma, VIPoma, glucagonoma, somatostatinoma), mucinous cystic neoplasm (MCN), acinar cell carcinoma
- see *Surgical Endocrinology*, GS65 for functional pancreatic neuroendocrine tumours

### Treatment

- resectable (10-20% of pancreatic cancer)
  - no involvement of liver, peritoneum, or vasculature (hepatic artery, SMA, SMV, portal vein, IVC, aorta), no distant metastasis
  - Whipple procedure (pancreaticoduodenectomy) for cure <5% mortality

  - distal pancreatectomy ± splenectomy, lymphadenectomy if carcinoma of midbody and tail of pancreas
  - adjuvant chemotherapy recommended (gemcitabine ± capecitabine, 5-FU/leucovorin)
- locally advanced, borderline resectable
  - tumours that abut the SMA, SMV, portal vein, hepatic artery, or celiac artery
- locally advanced, non-resectable (palliative → relieve pain, obstruction)
  - encasement of major vascular structures including arteries
  - most body/tail tumours are not resectable (due to late presentation)
  - relieve biliary/duodenal obstruction with endoscopic stenting or double bypass procedure (choledochoenterostomy + gastroenterostomy)
  - palliative chemotherapy (gemcitabine + nab-paclitaxel, FOLFIRNOX) ± radiotherapy

## Prognosis

- most important poor prognostic indicators are lymph node status, margin status, size >3 cm, perineural invasion (invasion of tumour into microscopic nerves of pancreas)
- overall 5 yr survival for all patients with pancreas cancer is 1%; following surgical resection 5 yr survival is 20%
- median survival for unresectable disease: 3-6 mo if metastatic, 8-12 mo if locally advanced at presentation

**Steps of a Whipple Resection (Pancreaticoduodenectomy)**

1. Assessment of metastatic disease (all peritoneal surfaces)
2. Mobilization of the duodenum and head of the pancreas
3. Identification of the superior mesenteric vein and mobilization of the pancreatic neck
4. Mobilization of the stomach; dissection of the hepatoduodenal ligament and cholecystectomy
5. Division of the stomach, proximal jejunum, and CBD
6. Transection of the pancreatic neck and dissection of the uncinate process from the retroperitoneum
7. Restoration of gastrointestinal continuity: construction of a pancreaticojejunostomy, hepaticojejunostomy, gastrojejunostomy using a neoduodenum

**Remove**

- CBD
- Gallbladder
- Duodenum
- Pancreatic head
- Distal stomach (sometimes)

**Table 26. TNM Classification System for Exocrine Tumours of the Pancreas (AJCC 8th edition)**

| Primary Tumour (T) | | Regional Lymph Nodes (N) | | Distant Metastasis (M) | |
|---|---|---|---|---|---|
| **TX** | Primary tumour cannot be assessed | **NX** | Regional lymph nodes cannot be assessed | **M0** | No distant metastasis |
| **T0** | No evidence of primary tumour | **N0** | No regional lymph node metastasis | **M1** | Distant metastasis |
| **Tis** | Carcinoma *in situ* | **N1** | Metastasis in one to three regional lymph nodes | | |
| **T1** | Tumour ≥2 cm in greatest dimension<br>T1a: <0.5 cm<br>T1b: 0.5-1.0 cm<br>T1c: 1.0-2.0cm | **N2** | Metastasis in four or more regional lymph nodes | | |
| **T2** | Tumour >2 cm and ≤4 cm in greatest dimension | | | | |
| **T3** | Tumour >4 cm in greatest dimension | | | | |
| **T4** | Tumour involves celiac axis, SMA, or common hepatic artery | | | | |

**Table 27. Staging and Treatment of Pancreatic Cancer**

| Stage | Classification | 5 Yr Survival | Treatment |
|---|---|---|---|
| **0** | Tis, N0, M0 | | Surgical resection ± chemotherapy |
| **IA** | T1, N0, M0 | 14% | Same as above |
| **IB** | T2, N0, M0 | 12% | Same as above |
| **IIA** | T3, N0, M0 | 7% | Same as above |
| **IIB** | T1-3, N1, M0 | 5% | Same as above |
| **III** | T1-3, N2, M0<br>T4, any N, M0 | 3% | Borderline resectable, trial of chemotherapy and radiation |
| **IV** | any T, any N, M1 | 1% | Non-resectable, palliative treatments |

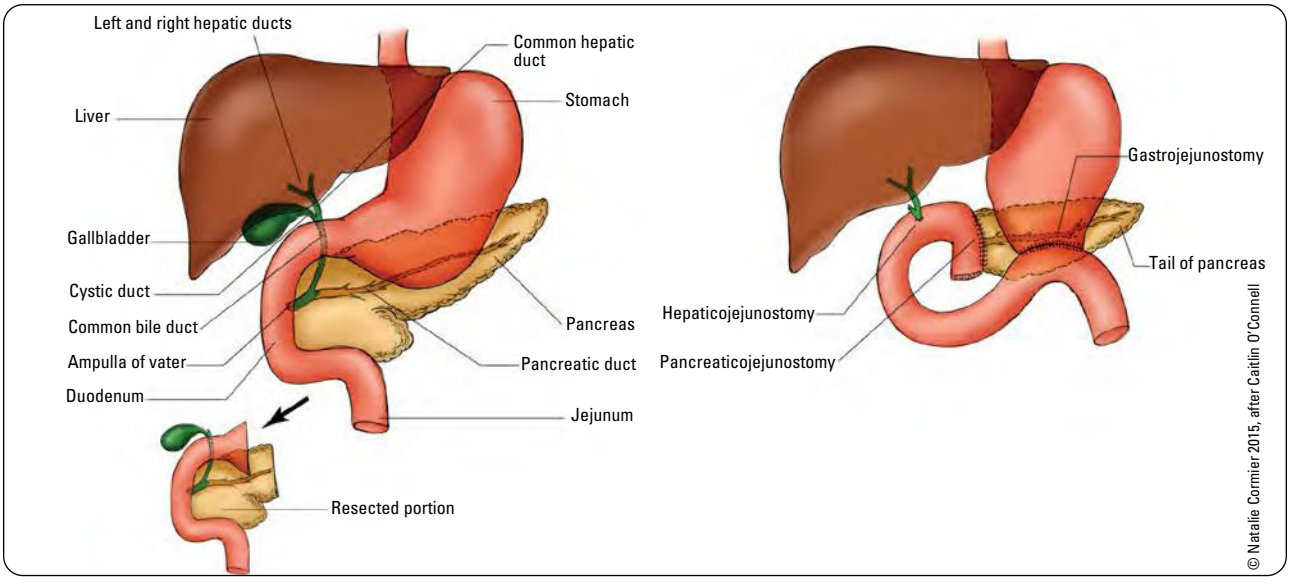



**Figure 26. Schematic of Whipple resection showing the resected components**

# Spleen

## Splenic Trauma

- typically from blunt trauma (especially in people with splenomegaly)
- most common intra-abdominal organ injury in blunt trauma
- may have Kehr's sign

**Kehr's Sign**
Left shoulder pain due to diaphragmatic irritation from splenic rupture, worsens with inspiration

### Treatment

- non-operative
  - in stable patients: extended bed rest with serial hematocrit levels, close monitoring for 3-5 d; pediatric guidelines for days of bed rest is grade plus 1 (i.e. grade 3 splenic laceration requires 4 d of bed rest)
  - hemostatic control
  - splenic artery embolization if patient stable and one of: active contrast extravasation, splenic pseudoaneurysm, hemoperitoneum
- operative
  - hemodynamically unstable patients with positive FAST will undergo operative surgical exploration
  - splenorrhaphy (suture of spleen) ± splenic wrapping with hemostatic mesh – if patient hemodynamically stable, patient has stopped bleeding and laceration does not involve hilum
  - partial splenectomy, rarely performed due to risk of recurrent hemorrhage
  - total splenectomy if patient unstable or high-grade injury

## Splenectomy

### Indications

- splenic trauma (most common reason for splenectomy), hereditary spherocytosis, primary hypersplenism, chronic immune thrombocytopenic purpura (ITP), splenic vein thrombosis causing esophageal varices, splenic abscess, thrombotic thrombocytopenic purpura (TTP), and sickle cell disease
- does not benefit all thrombocytopenic states (e.g. infection, most malignancies involving the bone marrow, drugs/toxins)
- probability of cure of ITP by splenectomy is 60-70%, may be predicted by response to IVIG

**Indication of Splenectomy**

**SHIRTS**
**S**plenic abscess/splenomegaly
**H**ereditary spherocytosis
**I**mmune thrombocytopenic purpura
**R**upture of spleen
**T**hrombotic thrombocytopenic purpura
**S**plenic vein thrombosis

### Complications

- short-term
  - injury to surrounding structures (e.g. gastric wall, tail of pancreas) and their vascular supply
  - post-operative thrombocytosis, leukocytosis
  - thrombosis of portal, splenic, or mesenteric veins
  - subphrenic abscess
- long-term
  - post-splenectomy sepsis (encapsulated organisms): 4% of splenectomized patients (highest risk in those <16 yr)
- 50% mortality
- prophylaxis with vaccinations, ideally 2 wk pre- or post-operative (*pneumococcal, H. influenzae*, and *meningococcus*)
- liberal use of penicillin especially in children <6 yr
  - splenosis: intra-abdominal "seeding" of splenic tissue during removal
  - increased risk of malignancy, DVT, and PE compared to non-splenectomized patients

## Splenic Infarct

### Pathophysiology

- splenic artery occlusion or oxygen-delivery insufficiency leading to parenchymal ischemia and necrosis
- can occur in sickle cell disease, thromboembolism, myelofibrosis, CML, hypercoagulable states
- patient can be asymptomatic or can have LUQ pain (70%), N/V, fever, chills, and Kehr sign

### Treatment

- non-operative: close follow-up, analgesia
- indications for splenectomy: complications such as rupture, abscess, persistent pseudocyst, bleeding, or sepsis

# Breast

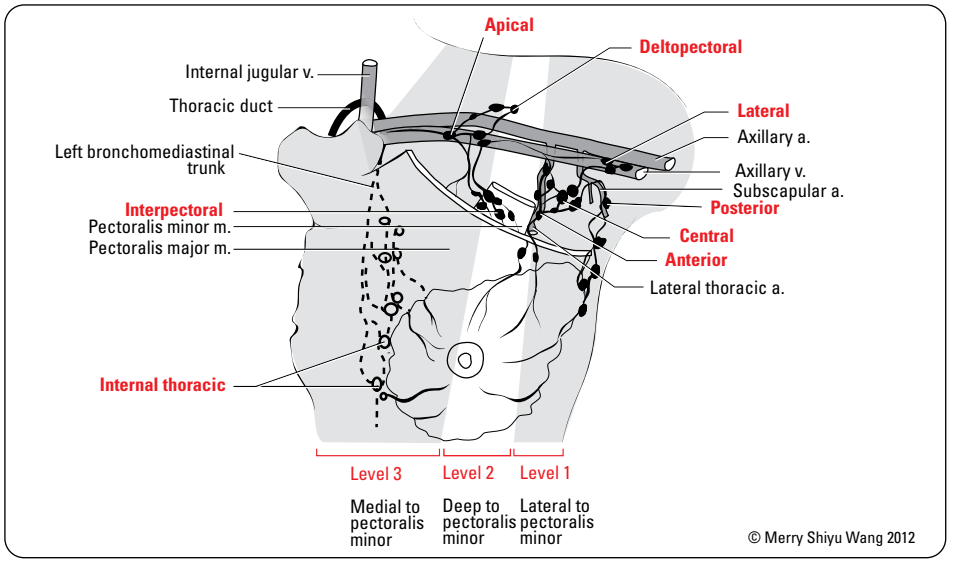



**Figure 27. Anatomy of the breast**

**Levels of Axillary Lymph Nodes**
**Level I:** lateral to pectoralis minor
**Level II:** deep to pectoralis minor
**Level III:** medial to pectoralis minor
(higher level of nodal involvement = worse prognosis)

# Benign Breast Lesions

## Three Categories

1. nonproliferative
2. proliferative without atypia
3. atypical hyperplasia

## NONPROLIFERATIVE LESIONS

- benign breast condition characterized by fibrous and cystic changes in the breast (fibrocystic changes/disease)
- most common: breast cysts
- other lesions include papillary apocrine change, epithelial-related calcifications and mild hyperplasia of the usual type
- no increased risk of breast cancer
- age 30 to menopause (and after if hormone replacement therapy (HRT) used)
- clinical features
  - breast pain, focal areas of nodularity or cysts often in the upper outer quadrant, frequently bilateral, mobile, varies with menstrual cycle, and nipple discharge (straw-like, brown, or green)
- treatment
  - evaluation of breast mass (U/S, mammography as indicated) and reassurance
  - analgesia (ibuprofen, ASA)
  - for severe symptoms: OCP, danazol, bromocriptine

**DDx for Breast Mass**
**Benign**
- Fibrocystic changes
- Fibroepithelial lesions (fibroadenoma most common; benign phyllodes)
- Fat necrosis
- Papilloma/papillomatosis
- Galactocele
- Duct ectasia
- Ductal/lobular hyperplasia
- Sclerosing adenosis
- Lipoma
- Neurofibroma
- Granulomatous mastitis (e.g. TB, granulomatosis with polyangiitis, sarcoidosis)
- Abscess
- Silicone implant

**Malignant**
- Breast cancer (likely invasive, DCIS rarely forms a breast mass)
- Malignant phyllodes
- Angiosarcoma (rare)

## PROLIFERATIVE LESIONS – WITHOUT ATYPIA

**Table 28. Proliferative Lesions - Without Atypia**

| | | Clinical Features | Diagnosis | Treatment | Risk of Breast Cancer |
|---|---|---|---|---|---|
| **Fibroadenoma** | Most common breast tumour in women <30 yr | Nodules: firm, rubbery, discrete, well-circumscribed, non-tender, mobile, hormone-dependent (unlike cysts), needle aspiration yields no fluid | Core or excisional biopsy sometimes required if concerned about malignancy U/S and FNA alone cannot differentiate fibroadenoma from phyllodes tumour | Generally conservative serial observation Consider excision if size 2-3 cm and growing on serial U/S (q6mo x 2 yr is usual follow-up), if symptomatic, formed after age 35, patient preference or features on core biopsy suggestive of a phyllodes tumour | Increased if complex, adjacent atypia or strong family history of breast cancer |
| **Intraductal Papilloma** | Solitary intraductal benign polyp | Can present as nipple discharge (most common cause of spontaneous, unilateral, bloody nipple discharge = pathologic nipple discharge), breast mass, nodule on U/S | | Surgical excision of involved duct to ensure no atypia | Can harbour areas of atypia or DCIS |
| **Usual Ductal Hyperplasia** | Increased number of cells within the ductal space | Incidental finding on biopsy of mammographic abnormalities or breast masses | | None required | Generally low risk, slightly increased if moderate or florid hyperplasia |
| **Sclerosing Adenosis** | Lobular lesion with increased fibrous tissue and glandular cells | Mass or mammographic abnormality | | None required | Low risk |

### ATYPICAL HYPERPLASIA
- can involve ducts (atypical ductal hyperplasia) or lobules (atypical lobular hyperplasia)
- cells lose apical-basal orientation
- increased risk of breast cancer
- diagnosis: core or excisional biopsy
- treatment: complete resection, risk modification (avoid exogenous hormones), close follow-up

### OTHER LESIONS

#### Fat Necrosis
- uncommon, result of trauma (may be minor, positive history in only 50%), after breast surgery (i.e. reduction)
- firm, ill-defined mass with skin or nipple retraction, ± tenderness
- regress spontaneously, but complete imaging ± biopsy to rule out carcinoma

#### Mammary Duct Ectasia
- obstruction of a subareolar duct (see Obstetrics, OB47)

#### Abscess
- lactational vs. non-lactational (periductal/subareolar) (see Obstetrics, OB47)

## Breast Cancer

#### Epidemiology
- leading cancer diagnosis in women in North America, 2nd leading cause of cancer mortality in women
- 1 in 8 (12.9% life time risk) women in Canada will be diagnosed with breast cancer in their lifetime
- 1 in 31 women in Canada will die from breast cancer
- all age relative survival is 87%



Gender followed by age are the two greatest risk factors for breast cancer

#### Risk Factors
- gender (99% female)
- age (83% >50 yr)
- personal history of breast cancer and/or prior breast biopsy (regardless of pathology)
- family history of breast cancer (greater risk if relative was first degree and premenopausal)
- high breast density, nulliparity, first pregnancy >30 yr, menarche <12 yr, or menopause >55 yr
- decreased risk with lactation, early menopause, and early childbirth
- radiation exposure (e.g. mantle radiation for Hodgkin's disease)
- >5 yr HRT use, >10 yr OCP use
- BRCA1 and BRCA2 gene mutations
- alcohol use, obesity, and sedentary lifestyle



Any palpable dominant breast mass requires further investigation

#### Male Breast Cancer (<1%)
- most commonly invasive ductal carcinoma
- often diagnosed at later stages
- stage-for-stage similar prognosis to breast cancer in females
- consider genetic testing: most often hormone receptor positive

#### Investigations
- mammography
  - indications: screening guidelines (see Family Medicine, FM3)
  - findings indicative of higher risk of malignancy
    - mass that is poorly defined, spiculated border
    - microcalcifications
    - architectural distortion
    - interval mammographic changes
  - normal mammogram does not rule out suspicion of cancer based on clinical findings
- other radiographic studies
  - U/S: differentiate between cystic and solid
  - MRI: high sensitivity, low specificity. Use annual MRI and mammography for patients with 25% lifetime risk of breast cancer
  - galactogram/ductogram (for nipple discharge): identifies lesions in ducts
  - metastatic workup indicated in Stage II-IV disease: bone scan, abdominal U/S, CXR (or CT chest/abdomen/pelvis), CT head (if specific neurological symptoms)

## Diagnostic Procedures

- "triple test" for diagnosis of breast cancer: clinical breast exam, imaging (U/S for <30 yr, mammography + U/S for >30 yr), pathology (biopsy)
- needle aspiration: for palpable cystic lesions; send fluid for cytology if blood or cyst does not completely resolve
- U/S or mammography guided core needle biopsy (most common)
- excisional biopsy: only performed as second choice to core needle biopsy; should not be done for diagnosis if possible



Diagnostic mammography is indicated in all patients, even in women <50 yr

## Genetic Screening

- consider testing for BRCA1/2 if:
  - young patient (<35 yr)
  - bilateral breast cancer in patients <50 yr
  - patient diagnosed with breast AND ovarian cancer
  - strong family history of breast/ovarian cancer
  - family history of male breast cancer



Phyllodes tumours are rare fibroepithelial breast tumours that can be benign or malignant that mostly affect women from 35-55 yr

## Staging

- patients are assigned a clinical stage pre-operatively (cTNM); following surgery the pathologic stage is determined (pTNM)
- clinical
  - tumour size by palpation, mammogram, U/S and/or MRI
  - nodal involvement by palpation, imaging
  - metastasis by physical exam, CXR, and abdominal U/S (or CT chest/abdomen/pelvis), bone scan (usually done post-operative if node-positive disease)
- pathological
  - tumour size and type
  - grade: modified Bloom and Richardson score (I to III) – histologic, nuclear, and mitotic grade
  - number of axillary nodes positive for malignancy out of total nodes resected, extranodal extension, and sentinel lymph node biopsy (SLNB) positive/negative
  - tumour biology: estrogen receptor (ER), progesterone receptor (PR), and HER2/neu oncogene status
  - margins: for invasive breast cancer negative margin is sufficient, for DCIS prefer 2 mm margin
  - lymphovascular invasion (LVI)
  - extensive *in situ* component (EIC): DCIS in surrounding tissue
  - involvement of dermal lymphatics (inflammatory) – automatically Stage IIIb

**Table 29. TNM Classification System for Staging of Breast Cancer (AJCC 2017)**

| Primary Tumour (T) | | Regional Lymph Nodes (N) | | Distant Metastasis (M) | |
|---|---|---|---|---|---|
| **TX** | Primary tumour cannot be assessed | **NX** | Regional lymph nodes cannot be assessed | **M0** | No distant metastasis |
| **T0** | No evidence of primary tumour | **N0** | No regional lymph node metastasis | **M1** | Distant metastasis |
| **Tis** | Ductal carcinoma *in situ* | **N1** | Involvement of 1-3 axillary lymph nodes and/or clinically negative internal mammary nodes on sentinel node biopsy | | |
| **T1** | Tumour ≤2 cm in greatest dimension | **N2** | Involvement of 4-9 axillary lymph nodes or clinically positive ipsilateral internal mammary lymph node | | |
| **T2** | Tumour >2 cm but ≤5 cm in greatest dimension | | | | |
| **T3** | Tumour >5 cm in greatest dimention | | | | |
| **T4** | Tumour of any size with direct extension to chest wall and/or skin | | | | |



| Favourable Features | Unfavourable Features |
|---|---|
| • <2 cm<br>• Grade I (low grade)<br>• Node negative<br>• ER positive<br>• Mucinous pattern | • >5 cm<br>• Grade III (high grade)<br>• Node positive<br>• ER negative<br>• Inflammatory cancer<br>• Her2Neu positive<br>• Positive margins<br>• Lymphovascular invasion<br>• Epidermal inclusion cyst<br>• Dermal lymphatics involved |

## Pathology

## NON-INVASIVE

### Ductal Carcinoma *in situ* (DCIS)

- proliferation of malignant ductal epithelial cells completely contained within breast ducts, often multifocal
- 80% non-palpable, detected by screening mammogram
- risk of invasive ductal carcinoma in same breast up to 35% in 10 yr
- treatment
  - lumpectomy with wide excision margins + radiation (5-10% risk of invasive cancer)
  - mastectomy if large area of disease, high grade, or multifocal (risk of invasive cancer reduced to 1%)
  - possibly tamoxifen as an adjuvant treatment
  - 99% 5 yr survival

### Lobular Carcinoma *in situ* (LCIS)
- neoplastic cells completely contained within breast lobule
- no palpable mass and no mammographic findings; usually incidental finding on breast biopsy for another indication
- LCIS is a risk factor for invasive carcinoma (approximately 1%/yr)
- treatment
  - if diagnosed on core biopsy, excisional biopsy necessary to rule out malignancy
  - if diagnosed on excisional biopsy, wide excision not needed since LCIS if often multicentric and not managed as precursor lesion
  - clinical follow-up and surveillance; consider chemoprevention (e.g. tamoxifen)

## INVASIVE

### Invasive Ductal Carcinoma (most common 80%)
- originates from ductal epithelium and infiltrates supporting stroma
- characteristics: hard, scirrhous, infiltrating tentacles, and gritty on cross-section
  - divided into three grades based on cytologic and architectural features: well differentiated (grade 1), moderately differentiated (grade 2), poorly differentiated (grade 3)

### Invasive Lobular Carcinoma (8-10%)
- originates from lobular epithelium, 20% bilateral
- subtle thickening originating from lobes/lobules; usually positive for estrogen and progesterone receptors
- harder to detect on mammography due to lack of microcalcifications (may benefit from MRI)

### Paget's Disease (1-3%)
- ductal carcinoma that invades nipple with scaling, and eczematoid lesion

### Inflammatory Carcinoma (1-3%)
- most aggressive form of breast cancer
- ductal carcinoma that grows in nests (vs. solid tumour); invades and blocks dermal lymphatics
- clinical features: erythema, skin edema, warm, swollen, and tender breast ± lump, nipple changes
- peau d'orange indicates advanced disease (IIIb-IV)

### Sarcomas: rare
- most commonly phyllodes tumour, a variant of fibroadenoma with potential for malignancy
- can also be angiosarcomas – after previous radiation

### Lymphoma: rare

### Other
- papillary, medullary, mucinous, and tubular cancers
- generally better prognosis

### Treatment

**Table 30. Breast Cancer Treatment by Stage**

| Stage | Primary Treatment Options | Adjuvant Systemic Therapy |
|---|---|---|
| **0 (*in situ*)**<br>Tis, N0, M0 | BCS + radiotherapy<br>BCS alone if margins >1 cm and low nuclear grade<br>Mastectomy* ± SLNB | Consider post-operative tamoxifen for ER+, trastuzumab for HER2+ |
| **I**<br>IA: T1, N0, M0<br>IB: T1, N1mi, M0 | BCS + axillary node dissection + radiotherapy<br>Mastectomy* + axillary node dissection/SLNB | May not be needed; discuss risks/benefits of chemotherapy and tamoxifen |
| **II**<br>A: T0, N1, M0<br>T1, N1, M0<br>T2, N0, M0<br>B: T2, N1, M0<br>T3, N0, M0 | BCS + axillary node dissection + radiotherapy<br>Mastectomy* + axillary node dissection/SLNB | Chemotherapy for premenopausal women or postmenopausal and ER negative, followed by tamoxifen if ER+ |
| **III**<br>A: T0, N2, M0<br>T1, N2, M0<br>T2, N2, M0<br>T3, N1, M0<br>T3, N2, M0<br>B: T4, N0, M0<br>T4, N1, M0<br>T4, N2, M0 | Likely mastectomy + axillary node dissection + radiotherapy after chemotherapy (neoadjuvant) | Neoadjuvant therapy should be considered (i.e. pre-operative) especially if not resectable chemotherapy and/or hormone therapy. Adjuvant radiation and chemotherapy may also be appropriate (i.e. post-operative) |
| **Inflammatory** | Mastectomy + axillary node dissection + radiotherapy | Neoadjuvant therapy |
| **IV**<br>any T, any N, M1 | Surgery as appropriate for local control | Primary treatment is systemic therapy (i.e. chemotherapy) and/or hormone therapy |

BCS = breast conserving surgery; SLNB = sentinel lymph node biopsy
*If no reason to select mastectomy, the choice between BCS + radiotherapy and mastectomy can be made according to patient's preference since choice of local treatment does not significantly affect survival if local control is achieved

**Diagnosis of Breast Lesions: Fine-Needle Aspiration Cytology (FNAC) or Core Needle Biopsy? A Review**
J Clin Pathol 2012;65:287-92
**CNB**
- High sensitivity (85%-100%) and specificity (86%-100%)
- High success rates for diagnosis of malignancy for palpable lesions (97%), non-palpable lesions (94%), and lesions <10 mm (90%)
- More accurate for histologic and immunohistochemistry examinations, and differentiation between *in situ* and invasive malignancies
- Reliable for testing of ER, PR, and HER2 status and proliferation assessment
- More painful procedure

**FNAC**
- Variable sensitivity (35%-95%) and specificity (48%-100%)
- Quality correlates with skill of aspirator
- Lower success rates for diagnosis of malignancy for palpable lesions (75-90%), non-palpable lesions (34-58%), and lesions <10 mm (50%)
- High rates of insufficient sampling for lesions >40 mm or calcified lesions
- Quick to perform
- Low technical costs

**Conclusions**: FNAC is preferable for palpable, low malignancy-risk lesions. However, for potential malignancies, CNB is advantageous with respect to prognostication and prediction and is likely cost-effective in the long-term

**Analysis of Circulating Tumour DNA to Monitor Metastatic Breast Cancer**
NEJM 2013;368:1199-1209
**Study**: The quantification of circulating tumour DNA, cancer antigen 15-3 (CA 15-3), and circulating tumour cells in 30 women with metastatic breast cancer receiving systemic therapy. The results were compared with radiographic imaging of tumours.
**Results/Conclusions**: Circulating tumour DNA was detected in 97% of women and showed greater correlation with changes in tumour burden than did CA 15-3 or circulating tumour cells, providing the earliest measure of treatment response in 53% of women. CA 15-3 and circulating tumour cells were detected in 78% and 87% of women, respectively. Circulating tumour DNA may therefore be an informative biomarker for metastatic breast cancer.

**10 Year Survival after Breast-Conserving Surgery Plus Radiotherapy Compared with Mastectomy in Early Breast Cancer in The Netherlands: A Population-Based Study**
Lancet Oncol 2016;17(8):1158
**Results/Interpretation**: Breast-conserving surgery plus radiotherapy showed improved 10 yr overall and relative survival compared with mastectomy in early breast cancer, but 10 yr distant metastasis-free survival was improved with breast-conserving surgery plus radiotherapy compared with mastectomy in the T1N0 subgroup only, indicating a possible role of confounding by severity. These results suggest that breast-conserving surgery plus radiotherapy is at least equivalent to mastectomy with respect to overall survival and may influence treatment decision making for patients with early breast cancer.

## PRIMARY SURGICAL TREATMENT

### Breast Conservation Surgery (BCS)
- lumpectomy must be combined with radiation for survival equivalent to mastectomy
- contraindications include
  - high risk of local recurrence (e.g. extensive malignant-type calcifications on mammogram), and multifocal primary tumours
  - failure to obtain tumour-free margins after re-excision
  - not suitable for radiation therapy (pregnancy, previous radiation, and collagen vascular disease)
  - large tumour size relative to breast

### Mastectomy
- radical mastectomy (rare): removes all breast tissue, skin, pectoralis muscle, and axillary nodes
- modified radical mastectomy (MRM): removes all breast tissue, skin, and axillary nodes
- simple mastectomy: removes all breast tissue and skin
- see Plastic Surgery PL37 for breast reconstruction

### Sentinel Lymph Node Biopsy (SLNB)
- performed in women with clinically node-negative invasive breast cancer and those with extensive DCIS who are undergoing mastectomy
- patients with clinically suspicious nodes should get U/S + FNA prior to decision to proceed with SLNB
- technetium-99 ± blue dye injected at tumour site prior to surgery to identify sentinel node(s)
- intra-operative frozen section evaluated can be considered
- proceed with ALND if >3 positive nodes, with 1-3 nodes whole breast radiation therapy may be alternative
- 5% false negative rate

### Axillary Lymph Node Dissection (ALND)
- perform in all patients with pathologic confirmation of nodal involvement (including positive SLNB as above)
- side effects: risk of arm lymphedema (10-15%) especially if getting radiation therapy, decreased arm sensation, and shoulder pain

## ADJUVANT/NEOADJUVANT

### Radiation
- indications
  - decrease risk of local recurrence; almost always used after BCS, sometimes after mastectomy
  - inoperable locally advanced cancer
  - axillary nodal radiation may be added if nodal involvement

### Hormonal
- indications
  - ER positive plus node-positive or high-risk node-negative
  - selective estrogen receptor modulators (SERM) if premenopausal (e.g. tamoxifen) or aromatase inhibitors if postmenopausal (e.g. anastrozole); optimal duration 5-10 yr
  - other options include ovarian ablation (e.g. goserelin/GnRH agonist, oophorectomy), progestins (e.g. megestrol acetate), and androgens (e.g. fluoxymesterone)
  - palliation for metastatic disease

### Chemotherapy
- indications
  - ER negative plus node-positive or high-risk node-negative
  - triple-negative disease (ER/PR and HER2-negative) - more common in younger and African-American women
  - ER positive and young age
  - stage I disease at high risk of recurrence (high grade, lymphovascular invasion)
  - palliation for metastatic disease
  - for HER2 positive breast cancer, add trastuzumab ± pertuzumab to the chemotherapy regimen

## FOLLOW-UP

### Post-Treatment Follow-Up
- assessment and physical exam q3-6mo x 3 yr, q6-12mo x 2 yr, and annually thereafter
- following BCS mammography q6-12mo; can reduce to annual once stable, no other routine imaging unless clinically indicated
- women who receive tamoxifen should have regular gynecologic follow-up (increased risk of endometrial cancer)



Breast conserving surgery can be offered to most women with stage I/II disease



There is no survival benefit of mastectomy over lumpectomy plus radiation for stage I and II disease



**Effect of Radiotherapy After Mastectomy And Axillary Surgery on 10 Year Recurrence and 20 Year Breast Cancer Mortality: Meta-Analysis of Individual Patient Data for 8135 Women in 22 Randomised Trials**
EBCTCG (Early Breast Cancer Trialists' Collaborative Group)
Lancet 2014;383(9935):2127-35
**Study**: Assessed the effect of radiotherapy in women with one to three positive lymph node after mastectomy and axillary dissection in a meta-analysis of 8135 women in 22 trials.
**Results**: For 700 women with axillary dissection and no positive nodes, radiotherapy had no significant effect on local regional recurrence, overall recurrence, or breast cancer mortality. For 1314 women with axillary dissection and one to three positive nodes, radiotherapy reduced local regional, overall recurrence, and breast cancer mortality.1133 of these 1314 women were in trials in which systemic therapy (cyclophosphamide, methotrexate, and fluorouracil, or tamoxifen) was given in both trial groups and radiotherapy again reduced local regional recurrence, overall recurrence, and breast cancer mortality. For 1772 women with axillary dissection and four or more positive nodes, radiotherapy reduced local regional recurrence, overall recurrence, and breast cancer mortality.
**Conclusion**: Post mastectomy and axillary dissection, radiotherapy reduced both recurrence and breast cancer mortality in the women with one to three positive lymph nodes in these trials even when systemic therapy was given.

### Local/Regional Recurrence
- recurrence in treated breast or ipsilateral axilla
- 1% per yr up to maximum of 15% risk of developing contralateral malignancy
- 5x increased risk of developing metastases

### Metastasis
- bone > lungs > pleura > liver > brain
- treatment is palliative: hormone therapy, chemotherapy, radiation
- overall survival of metastatic breast cancer is 36-60 mo

# Surgical Endocrinology

## Thyroid and Parathyroid

- see Endocrinology, E21

### Thyroidectomy
- indications: thyroid cancer, large or symptomatic thyroid goitre, toxic nodules, or some patients with Graves' disease (not candidates for RAI)
- pre-operative workup: thyroid U/S for thyroid nodules, FNA for nodules ≥1 cm with suspicious U/S features or for most nodules ≥1.5 cm with low suspicion U/S features, and CT neck for preoperative staging when advanced disease is suspected
- complications
  - lobectomy: recurrent laryngeal nerve palsy (hoarseness or swallowing issues), neck hematoma
  - total thyroidectomy: same as above plus hypoparathyroidism/hypocalcemia, bilateral RLN palsy (requiring tracheostomy)
  - 20-60% of patients need thyroxine after lobectomy and 100% need thyroxine after total thyroidectomy

### Parathyroidectomy
- indications: symptomatic primary hyperparathyroidism due to effects of PTH on bone or kidneys, asymptomatic primary hyperparathyroidism with specific laboratory criteria (elevated serum $Ca^{2+}$, marked hypercalciuria, Cr clearance <30% normal, bone density reduction with T score <2.5, <50 yr)
- contraindications: familial hypocalciuric hypercalcemia
- pre-operative workup: 99mTc sestamibi scanning, ± SPECT or CT, U/S
- complications: recurrent/superior laryngeal nerve injury, post-operative hypocalcemia, infection, and bleeding

## Adrenal Gland

- see Endocrinology, E30
- functional anatomy
  - cortex: glomerulosa (mineralocorticoids), fasciculata (glucocorticoids), and reticularis (sex steroids)
  - medulla: catecholamines (epinephrine, norepinephrine)
- types of adrenal tumours: functional (e.g. Cushing's syndrome, Conn's syndrome, pheochromocytoma) or non-functional

### INCIDENTALOMA
- adrenal mass discovered by investigation of unrelated symptoms

### Epidemiology
- benign adenoma (38%) > metastases to adrenal (22%) >> cyst, carcinoma, pheochromocytoma, neuroblastoma
- metastasis to adrenal gland from: lung > breast, colon, lymphoma, melanoma, and kidney
- peak incidence of carcinoma: females age 50-60, risk decreases with increasing age and male gender

### Investigations
- MRI, CT: size >6 cm is best predictor of primary adrenal carcinoma (92% are >6 cm)
- functional studies
  - pheochromocytoma: plasma metanephrines (highly specific and sensitive). If not available, 24 h urine catecholamines
  - Cushing's: 24 h urine cortisol or 1 mg overnight dexamethasone suppression test
  - aldosteronoma: electrolytes, aldosterone, plasma renin activity level, saline suppression test if appropriate
  - adrenal androgens: 17-OH progesterone and dehydroepiandrosterone (DHEAS)
- FNA biopsy: usually not recommended. May be helpful in situations when diagnostic uncertainty for metastasis

### Treatment
- functional tumour: resect
- non-functional tumour
  - >4 cm: resect
  - <4 cm: follow-up imaging in 6-12 mo, resect if >1 cm enlargement

# Pancreas

## INSULINOMA
- tumour that secretes insulin
- most common pancreatic endocrine neoplasm; 10% associated with MEN1 syndrome

### Clinical Features
- Whipple's triad
- palpitations, trembling, diaphoresis, confusion, seizure, and personality changes

### Investigations
- blood work: decreased serum glucose and increased serum insulin and C-peptide, pro-insulin
- U/S, CT: insulinomas evenly distributed throughout head, body, tail of pancreas

### Treatment
- only 10% are malignant
- enucleation of solitary insulinomas may be done endoscopically
- tumours >2 cm located close to the pancreatic duct may require pancreatectomy or pancreaticoduodenectomy

**Whipple's Triad**
- Symptomatic fasting hypoglycemia
- Serum glucose <2.8 mmol/L
- Relief of symptoms when glucose is administered

## GASTRINOMA
- tumour secreting gastrin; cause of Zollinger-Ellison syndrome

### Clinical Features
- abdominal pain, PUD, severe esophagitis
- multiple ulcers in atypical locations refractory to antacid therapy

### Investigations
- blood work: serum gastrin levels (usually >1000 pg/mL), secretin stimulation test
- U/S, CT: 70-90% found in Passaro's triangle (head of pancreas medially, 2nd portion of duodenum inferiorly, and the confluence of the cystic and CBD superiorly)
- octreotide scintigraphy scan

### Treatment
- 50% are malignant
- surgical resection of tumour dependent on location
- non-surgical treatment: chemotherapy, somatostatin analogues, interferon, and chemoembolization
- if inoperable, vagotomy can be performed for symptomatic control

**Zollinger-Ellison Syndrome**
Occurs because of gastric acid hypersecretion; patient experiences diarrhea and abdominal pain, as well as peptic disease and reflux disease

## VASOACTIVE INTESTINAL PEPTIDE-SECRETING TUMOUR
- tumour secreting VIP; commonly located in the distal pancreas and most are malignant when diagnosed

### Clinical Features
- severe watery diarrhea causing dehydration, weakness, and electrolyte imbalance

### Investigations
- blood work: serum VIP levels
- U/S, CT

### Treatment
- somatostatin analogues
- surgical resection/palliative debulking

**Hypertrophic Pyloric Stenosis**
Non-bilious emesis in infants is the classic presentation

**Rule of 2s for Meckel's Diverticulum**
- **2**% of the population
- **2**:1 male-to-female ratio
- Symptomatic in **2**% of cases
- Found within **2** feet (10-90 cm) of the ileocecal (IC) valve
- **2** inches in length
- **2** inches in diameter
- **2** types of tissue (gastric, pancreatic)
- Often present by **2** yr of age

# Pediatric Surgery

| Condition | Epidemiology and Risk Factors | Pathophysiology | Clinical Features and History | Physical Exam | Investigations | Treatment | Prognosis |
|---|---|---|---|---|---|---|---|
| **Hydrocele** (see Urology, U31) | 1-2% of live births<br>Present at birth, majority close spontaneous by 1 yr<br>M:F = 6:1<br>Prematurity | **Communicating hydroceles**: processus vaginalis fails to close with small opening for fluid to move freely between peritoneal cavity through patent processus (if opening progresses to allow passage of intestine, it is a hernia)<br>**Noncommunicating hydroceles**: fluid trapped in tunica vaginalis; in older children, may be secondary to testicular pathology (reactive hydrocele) | Painless scrotal mass<br>Communicating hydroceles increase in size with standing or valsalva, may be absent in the morning and large in the evening | Transillumination suggests hydrocele<br>Silk glove sign: gently palpating hydrocele sac over pubic tubercle feels like rubbing silk on silk | U/S if suspect pathology | Most resolve spontaneously by 1 yr<br>Surgical repair if:<br>Persistence >2 yr<br>Pain<br>Fluctuating in size which suggests communication<br>Cosmetic reasons<br>Infection | <2% recurrence |
| **Hypertrophic Pyloric Stenosis** | 0.03-1.0% of live births<br>Can present at 1-20 wk, most commonly at 6-8 wk<br>M:F = 4:1<br>Early erythromycin exposure (<13 d old) | Acquired pyloric circular muscle hypertrophy results in gastric outlet obstruction<br>Hypovolemia caused by emesis of gastric contents causes hypochloremic, hypokalemic, metabolic alkalosis<br>Electrolyte exchange based volume retention in kidneys results in paradoxical aciduria | Projectile non-bilious vomiting<br>Vomiting 30-60 min after feeds<br>Hungry after vomiting<br>Dehydration (variable severity) | Smooth oblong 1-2 cm mass palpable above umbilicus, "olive" visible left-to-right gastric contraction "waves" after feeding | Electrolytes (assess hypochloremia, dehydration)<br>U/S shows pyloric length >14 mm, muscle thickness >4 mm<br>Upper GI series necessary only when U/S unavailable or non-diagnostic will show "string sign" | Fluid resuscitate with normal saline, correct electrolyte and acid/base abnormalities with D5, 1/2NS + 20 mEq/L KCl at maintenance rate<br>NGT decompression unnecessary<br>Pyloromyotomy, open (Ramstedt vs. transumbilical or laparoscopic approach)<br>Alternative therapies such as TPN/wait or atropine impractical due to long time course of effect | Pyloromyotomy curative |
| **Congenital Diaphragmatic Hernias**<br>3 types:<br>Posterolateral (Bochdalek)<br>Left-sided, 85%<br>Right-sided, 13%<br>Bilateral, rare, often fatal<br>Anterior (Morgagni)<br>Hiatus | 1 in 2000 to 5000 live births<br>Presents within hours of life although some cases of delayed presentation<br>M=F<br>>10% are associated with other congenital anomalies<br>Prenatal diagnosis common | **Left-sided**: small bowel, large bowel, stomach, and solid viscera (spleen, left lobe of liver) herniate into thorax<br>**Right-sided**: liver, large bowel herniate into thorax<br>Pulmonary hypoplasia<br>Pulmonary HTN | Early respiratory distress<br>Cyanosis<br>Scaphoid abdomen<br>Prenatal diagnosis | Decreased air entry ± bowel sounds in the chest<br>Displaced heart sounds | Prenatal US/MRI<br>ABG<br>CXR (bowel loops in hemithorax, shifted heart)<br>Echocardiography<br>Genetic consultation if warranted | Intubate<br>Orogastric suction<br>Period of respiratory stabilization due to associated pulmonary hypoplasia (may require extracorporeal membrane oxygenation)<br>Surgical repair after stable by hernia reduction and closure of diaphragmatic defect – open vs. thoracoscopic vs. laparoscopic with or without prosthetic or muscular patch depending on size of defect | Better outcomes in later presentations<br>Hearing deficit (40%)<br>Associated GERD<br>MSK defects – chest wall and scoliotic defects a potential complication of thoracotomy<br>Long-term surveillance for potential recurrence<br>Failure to thrive<br>Chronic lung disease if severe hypoplasia |
| **Meckel's Diverticulum**<br>Most common remnant of vitelline duct that connects yolk sac with primitive midgut | 1-3% of population<br>M:F = 3:1<br>Present most frequently during first 5 yr of life<br>Symptomatic in 2% of cases | Failure of vitelline duct to regress 5-7 wk in utero; 50% contain heterotopic tissue (e.g. gastric mucosa, ectopic pancreas); other associated anomalies include omphalomesenteric fistula, umbilical sinus, umbilical cyst, fibrous band | BRBPR (heterotopic gastric mucosa in Meckel's causing mucosal ulceration and bleeding in adjacent small bowel mucosa)<br>Abdominal sepsis (Meckel's diverticulitis ± perforation)<br>Small bowel volvulus around fibrous band | Tenderness (lower abdomen) near umbilicus | AXR<br>Meckel scan: scan for ectopic gastric mucosa with technetium Tc99m pertechnetate IV (sensitivity 85%, specificity 95%) | Stabilize, resection by laparotomy or laparoscopy ± incidental appendectomy | Resection curative |

| Condition | Epidemiology and Risk Factors | Pathophysiology | Clinical Features and History | Physical Exam | Investigations | Treatment | Prognosis |
|---|---|---|---|---|---|---|---|
| **Malrotation** | 1:500 live births<br>1/3 present by 1 wk of age, 3/4 by 1 mo of age, 90% by 1 yr of age<br>M:F = 1:1; higher incidence among patients with cardiac anomalies, heterotaxy syndromes | Failure of gut to normally rotate around SMA with associated abnormal intestinal attachments and anatomic positions<br>Represent a spectrum of rotational abnormalities including complete non-rotation (which is not at high risk for volvulus) | Bilious emesis is the cardinal sign, especially if abdomen nondistended<br>If bilious emesis in ill child with distended abdomen, consider surgical exploration to rule out volvulus<br>Rectal bleed (late/ominous signs)<br>Intermittent symptoms | Bilious drainage from NGT<br>Tachycardic, pale<br>Diaphoretic<br>Flat abdomen<br>Tenderness | AXR: obstruction of proximal SBO, double-bubble sign, intestinal wall thickened<br>Immediate UGI: dilated duodenum, duodenojejunal segment (Ligament of Treitz) right of midline and not fixed posteriorly over spinal column, "corkscrew" sign indicating volvulus<br>U/S: "whirlpool" sign, abnormal SMA/SMV relationship indicates<br>UGI to rule out rotational anomalies | IV antibiotics<br>Fluid resuscitation<br>EMERGENT LAPAROTOMY<br>Ladd procedure: counterclockwise reduction of midgut volvulus, division of Ladd's bands, division of peritoneal attachments between cecum and abdominal wall that obstruct duodenum, broadening of the mesentery (open folded mesentery like a book and divide congenital adhesions), ± appendectomy<br>Positioning the bowel into non-rotation (SBO in right abdomen, LBO in left abdomen) | Mortality related to length of bowel loss: 10% necrosis – 100% survival rate, 75% necrosis – 35% survival rate<br>Recurrence 2-6% |
| **Gastroschisis** | 1:2000 live births<br>Antenatal diagnosis common<br>Increases with younger maternal age and associated with IUGR<br>M:F = 1:1 | Defect of abdominal wall, with free extrusion of intestine into amniotic cavity<br>No specific environmental factor identified<br>Defect in embryogenesis unclear | Not associated with genetic syndromes<br>10% with intestinal atresia<br>Some cases associated with short bowel syndrome due to antenatal volvulus and necrosis of herniated bowel | Hollow viscera (stomach, small and large bowels)<br>Defect lateral to cord (usually right)<br>Bowel may be inflamed, thickened, matted, foreshortened<br>Defect size variable | Prenatal U/S<br>Elevated MS-AFP | NGT decompression<br>IV fluids<br>IV antibiotics<br>Keep viscera moist and protected until surgical reduction with primary abdominal closure or staged closure with silo<br>May have bowel dysmotility requiring motility medications | >90% survival rate |
| **Omphalocele** | 1:5000 live birth<br>Antenatal diagnosis common<br>Lower gestational age<br>Increased maternal age<br>M:F = 1.5:1 | Defect of abdominal wall and umbilical ring, with extrusion of sac covered viscera (amnion, Wharton's jelly, peritoneum)<br>Duhamel's theory – failure of body wall morphogenesis<br>Commonly associated with rotational abnormalities of the intestine | 30-70% associated with genetic syndromes (e.g. Pentalogy of Cantrell, congenital heart disease, Beckwith-Wiedemann syndrome, Trisomy 18)<br>Associated pulmonary hypoplasia | Hollow viscera (stomach, small and large bowels, often liver)<br>Sac present with cord attached | Prenatal U/S<br>Elevated MS-AFP | NGT decompression<br>IV fluids, IV antibiotics<br>Small defect (<2 cm): Primary closure<br>Medium (2-4 cm) and large (>4 cm) defects: silver sulfadiazine coupled with compression dressing (to allow epithelialization and gradual reduction) or Silon Silo Pouch, followed by future repair ±mesh | 40-70% survival rate<br>Higher survival rates most likely related to antenatal mortality of fetuses with giant omphaloceles |
| **Umbilical Hernias** | Incidence 2-14%<br>Increases with prematurity<br>Decreases with increasing age | Incomplete closure of peritoneal and fascial layers within umbilicus by 4 yr<br>Hernia is peritoneum-lined and skin-covered<br>Size of fascial defect determines chances of spontaneous closure | Majority asymptomatic<br>Majority (95%) spontaneously resolve by age 4<br>Incarceration prior to age 5 very rare<br>Most symptoms occur in late adolescence or adulthood | Protrusion from umbilicus<br>Different from less common abdominal wall hernias that do not spontaneously resolve (e.g. epigastric hernias)<br>Most defects >1.5 cm in infancy will not close spontaneously | None if uncomplicated | Repair if not spontaneously closed by age 5<br>Earlier repair of large "proboscoid" hernias with extensive skin stretching may be warranted for cosmetic reasons<br>Simple primary closure of fascial defect | Almost never become incarcerated<br>Low risk of recurrence |
| **Intestinal Atresia** | Incidence 2-14%<br>May be antenatally diagnosed by dilated bowel loops or "double-bubble" sign on x-ray for duodenal atresia<br>Decreased with increasing age | Duodenal – failure of bowel to recanalize after endodermal epithelium proliferation (wk 8-10)<br>Jejunal/ileal – acquired as a result of vascular disruption → ischemic necrosis → resorption of necrotic tissue → blind distal and proximal ends<br>Colonic – mechanism unknown, thought to be similar to small bowel atresia | Gastric distension and vomiting (usually bilious)<br>Duodenal – may be associated with other anomalies (tracheoesophageal fistula, cardiac, renal, and vertebral anomalies), 24-28% have Down syndrome<br>Jejunal/ileal – within 2 d of birth, may be associated with CF<br>Colonic – within 3 d of birth | Complete physical<br>Special attention to abdominal exam<br>Perineum and anus<br>Include evaluation of respiratory distress and signs of volume depletion<br>Congenital anomalies<br>Jaundice | Contrast enema ± UGI with small bowel follow through (SBFT)<br>Group and screen<br>INR and PTT if for surgery | NPO<br>NGT decompression<br>Fluid resuscitate<br>TPN<br>Broad spectrum antibiotics<br>Duodenal – duodenoduodenostomy or duodenojejunostomy<br>Jejunal/ileal – primary anastomosis; or if atresia associated with short bowel then may create end stoma or defer surgery for bowel lengthening procedures<br>Colonic – primary anastomosis | Long-term survival<br>Duodenal – 86%<br>Jejunal/ileal – 84%<br>Colonic – 100% |

| Condition | Epidemiology and Risk Factors | Pathophysiology | Clinical Features and History | Physical Exam | Investigations | Treatment | Prognosis |
|---|---|---|---|---|---|---|---|
| **Hirschsprung's Disease** | 1:5000 births<br>M:F = 3:1 to 4:1, approaches 1:1 when whole colon involved<br>Can have aganglionosis of small bowel as well<br>Familial Hirschsprung's in <5% of cases | Defect in migration of neurocrest cells to intestine resulting in aganglionic bowel that fails to peristalse and internal sphincter that fails to relax (internal anal sphincter achalasia) causing functional and partial mechanical obstruction, respectively;<br>always starts in the rectum and variable involvement proximally;<br>RET mutation | Failure to pass meconium spontaneously within 48 h of life is the classic history (95% pass meconium within 24 h, 5% within 48 h)<br>Symptoms of bowel obstruction: abdominal distension, constipation, bilious emesis<br>Enterocolitis/sepsis<br>Failure to thrive | ± abdominal distension<br>Squirt/blast sign | Rectal biopsy (gold standard) – look for aganglionosis and neural hypertrophy<br>AXR<br>Contrast enema to find narrow rectum and transition zone<br>Anal manometry unreliable in infants – classic finding is absence of rectoanal inhibitory reflex | Duhamel pull-through procedure: surgical resection of aganglionic intestinal segment and anastomosis of remaining intestine to anus<br>Either in newborn period or staged if extensive aganglionosis | Most have normal/near-normal anorectal function<br>Complications: fecal incontinence and constipation, post-operative enterocolitis (medical emergency if progresses to sepsis) |
| **Cryptorchidism** | 2-5% of term males – most of these descend spontaneously by 6 mo of age<br>1% of males do not spontaneously descend<br>Suspect in prematurity | Idiopathic<br>Descent is mediated by descendin which is created in response to testosterone<br>Descent usually begins at 28 wk | Palpable testicle within inguinal canal or testicle which can be milked down into the scrotum (called retractile testis)<br>Occasionally no palpable testis as it is intra-abdominal<br>Consider other congenital abnormalities | Scrotal asymmetry<br>Bi-annual testicular exam with palpation<br>Distinguish truly undescended testis from retractile testis (which is "high" testis due to hyperactive cremasteric muscles) | Depends on age of presentation<br>Older child: LH, FSH, Müllerian inhibiting substance, hCG stimulation test for gonadotropin production<br>Infant: U/S, FSH, LH, karyotype, MIS, 17-hydroxy-progesterone<br>If non-palpable: Exam under anesthesia, exploratory laparoscopy | hCG to stimulate testosterone production and descent<br>Orchidopexy – especially if undescended by age 6 mo-2 yr | Orchidopexy<br>Decreased risk of torsion and blunt trauma to testicle<br>No effect on malignant potential of testicle<br>Descent can preserve spermatogenesis if performed by 1 yr |
| **Intussusception** | Most common cause of bowel obstruction between 6-36 mo<br>26:100,000 newborns<br>M:F = 3:2<br>Pathologic lead points: enlarged Peyer's patches due to viral infections of the GI tract, polyps, Meckel's diverticulum CF, lymphoma, IBD may increase risk | Idiopathic is most common<br>Usually starts at ileocecal junction<br>Telescoping of bowel into itself causing an obstruction and vascular compromise | Acute onset of abdominal pain which is classic episodic "colicky" pain<br>Vomiting ± bilious<br>Abdominal mass<br>Currant-jelly stool suggests mucosal necrosis and sloughing | Abdominal exam<br>Palpate for masses (especially sausage shaped upper abdominal mass) and tenderness<br>Signs of bowel obstruction: distended abdomen<br>Look for localized peritonitis which suggests transmural ischemia | AXR for signs of bowel obstruction or perforation<br>U/S if suspect pathology | If peritonitis, then consider operative management<br>Non-operative management involves reduction via air contrast enema<br>Operative reduction can be done open or laparoscopically<br>Resection of involved colon if failure to reduce or bowel appears compromised | 10% recurrence rate<br>If recurrent = more likely non-idiopathic<br>If successfully reduced by enema in older children allow 2 wk resolution of edema then perform SBFT to rule out pathologic lead points |
| **Tracheoesophageal Fistula (TEF)** | 1:3000-1:4500 | Associated anomalies in 50%: VACTERL association | Varies with type of fistula<br>May have history of maternal polyhydramnios<br>May present after several months (if no associated esophageal atresia) of non-bilious vomiting, coughing, cyanosis with feeds, respiratory distress, recurrent pneumonia, frothy bubbles of mucus in mouth, and nose that return after suctioning | | X-ray: anatomic abnormalities, NGT curled in pouch | Investigate for other congenital anomalies, early repair by surgical ligation to prevent lung damage and maintain nutrition and growth | Complications: pneumonia, sepsis, reactive airways disease<br>Following repair: esophageal stenosis and strictures at repair site, GERD and poor swallowing (i.e. dysphagia, regurgitation) |
| **Inguinal Hernias** | 5% of all term newborns<br>2x risk and more likely bilateral if pre-term<br>M:F = 4:1<br>Low birth weight increases risk<br>1/5 inguinal hernias will become incarcerated if patient is <1 yr<br>Incarceration is more common in females<br>Associated with other conditions: androgen insensitivity, connective tissue diseases | All infant hernias are indirect: descent of intra-abdominal contents through the internal inguinal ring through a patent tunica vaginalis<br>Inguinal hernia can be reducible, incarcerated (unreducible), or strangulated | Most common presentation: painless intermittent mass in groin, may also note extension into scrotum (scrotal mass in absence of inguinal mass is a hydrocele)<br>If incarcerated: tender, vomiting, firm mass, erythema then cyanosis of mass may be noted | Palpate for "bag of worms" suggests possible testicular varicocele<br>Biannual testicular exam + palpation along inguinal canal to evaluate for any masses<br>"Silk sign" – palpable thickening of cord<br>Mass palpated at external inguinal ring and reducible through inguinal canal into abdomen<br>Must always try reduction to confirm that hernia is not incarcerated | Physical exam is gold standard<br>U/S only if physical exam uncertain (e.g. in small infants where exam can be difficult) | Manual reduction – in the ER to relieve acute symptoms (then repair)<br>For reducible hernia: repair within a few weeks (if <1 yr) vs. elective repair (if >1 yr)<br>For incarcerated hernia: repair immediately (emergency)<br>Herniorraphy – definitive treatment by reduction of herniated contents and high ligation of sac for indirect hernias<br>Laparoscopic or open techniques | Risk of recurrence after surgical reduction <3% but higher if repair done in premature infants or if hernia was incarcerated/strangulated at repair |



All inguinal hernias of infancy and childhood require repair at the earliest convenience; emergent repair if incarcerated/strangulated

# Skin Lesions

- see Dermatology, D5; Emergency Medicine, ER43; Plastic Surgery, PL5

# Common Medications

| | |
|---|---|
| **Antiemetics** | • dimenhydrinate (Gravol®) 25-50 mg PO/IV/IM q4-6h prn<br>• prochlorperazine (Stemetil®) 5-10 mg PO/IV/IM bid-tid prn<br>• metoclopramide (Maxeran®) 10 mg IV/IM q2-3h prn, 10-15 mg PO qid (30 min before meals and qhs)<br>• ondansetron (Zofran®) 4-8 mg PO q8h prn<br>• granisetron (Kytril®) 1 mg PO bid (for nausea from chemotherapy/radiation) |
| **Analgesics** | • acetaminophen ± codeine (Tylenol® #3/plain) 1-2 tabs q4-6h PO/PR prn<br>• hydromorphone 1-2 tabs PO q4h prn, 0.5-2 mg IV q3-4h prn<br>• ibuprofen 200-400 mg PO q4-6h prn<br>• morphine 2.5-10 mg IM/SC q4-6h prn + 1-2 mg IV q1h prn for breakthrough<br>• ketorolac (Toradol®) 30-60 mg IM/IV q6h prn<br>• acetominophen/oxycodone (Percocet® ) 325/5 mg, 1-2 tabs PO q4-6h prn |
| **DVT Prophylaxis** | • heparin 5000 units SC bid, if cancer patient then heparin 5000 units SC tid/bid<br>• dalteparin (Fragmin®) 5000 units SC daily<br>• enoxaparin (Lovenox®) 40 mg SC daily |
| **Antidiarrheals** | • loperamide (Imodium®) 4 mg PO initially, then 2 mg PO after each loose stool up to 16 mg/d<br>• diphenoxylate + atropine (Lomotil®) 2 tabs/10 mL PO qid |
| **Laxatives** | • sennosides (Senokot®) 1-2 tabs qhs<br>• docusate sodium (Colace®) 100 mg PO bid<br>• glycerine suppository 1 tab PR prn<br>• lactulose 15-30 mL PO qid prn<br>• milk of magnesia (MOM) 30-60 mL PO qid prn<br>• bisacodyl (Dulcolax®)10-15 mg PO prn |
| **Sedatives** | • zopiclone (Imovane®) 5-7.5 mg PO qhs prn<br>• lorazepam (Ativan®) 0.5-2 mg PO/SL qhs prn |
| **Antibiotics** | • cefazolin (Ancef®) 1 g IV/IM on call to OR or q8h – GP except *Enterococcus*, GN only *E. coli, Klebsiella*, and *Proteus*<br>• cefalexin (Keflex®) 250-500 mg PO qid – *Listeria*, GP except *Enterococcus*, GN only *E. coli, Klebsiella*, and *Proteus*<br>• ceftriaxone 1-2 g IM/IV q24h – broad coverage including *Pseudomonas*<br>• ampicillin 1-2 g IV q4-6h – *Listeria*, GP (*Enterococcus*) except *Streptococcus* and *E. coli*, oral anaerobes except *Bacteroides*<br>• gentamicin 3-5 mg/kg/d IM/IV divided q8h; monitor creatinine, gentamicin levels – GN including *Pseudomonas*<br>• ciprofloxacin 400 mg IV q12h, 500 mg PO bid – GN including *Pseudomonas*<br>• metronidazole (Flagyl®) 500 mg PO/IV bid (500 mg PO tid for *C. difficile*) – anaerobes<br>• clindamycin 600-900 mg IV q8h, 150-400 mg PO qid – GP except *Enterococcus*, anaerobes<br>• piperacillin/tazobactam 4.5 mg IV q6h – GP, GN, and anaerobes<br>• vancomycin 1g IV q12h – GP and MRSA<br>• sulfamethoxazole/trimethoprim DS (Septra®) PO bid – GP, GN including *Nocardia* |
| **Over-the-Counter Medications** | • bismuth subsalicylate (Pepto-Bismol®) 2 tabs or 30 mL PO q30min-1h up to 8 doses/d<br>side effects: black stools, risk of Reye's syndrome in children<br>• ASA + citrate + bicarbonate (Alka-Seltzer®) 2 tabs in 4 oz water PO q4h prn, max 8 tabs<br>• aluminum hydroxide + magnesium hydroxide (Maalox®) 10-20 mL or 1-4 tabs PO prn<br>• calcium carbonate (Tums®) 1-3 g PO q2h prn<br>• calcium carbonate and magnesium hydroxide (Rolaids®) 2-4 tabs PO q1h prn, max 12 tabs/d |

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# GM Geriatric Medicine

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# Acronyms

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ACEI | angiotensin converting enzyme inhibitor | CVA | cerebrovascular accident | IBD | inflammatory bowel disease | PCI | percutaneous coronary intervention |
| ADL | activities of daily living | CXR | chest x-ray | IBS | irritable bowel syndrome | POA | power of attorney |
| ADR | adverse drug reaction | dBP | diastolic blood pressure | ICP | intracranial pressure | PPI | proton pump inhibitor |
| ARB | angiotensin receptor blocker | DM | diabetes mellitus | IV | intravenous | PPS | palliative performance scale |
| BMI | body mass index | DNR | do not resuscitate | INR | international normalized ratio | PTH | parathyroid hormone |
| BP | blood pressure | ESAS | Edmonton Symptom Assessment Scale | LOC | level of consciousness | PSW | personal support worker |
| BPH | benign prostatic hypertrophy | | | LV | left ventricle | RA | rheumatoid arthritis |
| BUN | blood urea nitrogen | GABA | gamma-aminobutryic acid | MMSE | Mini Mental Status Examination | sBP | systolic blood pressure |
| CBC | complete blood count | GCA | giant cell arteritis | MS | multiple sclerosis | SNRI | serotonin-norepinephrine reuptake inhibitor |
| CBT | cognitive behavioural therapy | GERD | gastroesophageal reflux disease | NE | norepinephrine | | |
| CHF | congestive heart failure | GFR | glomerular filtration rate | NG | nasogastric | SSRI | selective serotonin reuptake inhibitor |
| CKD | chronic kidney disease | GI | gastrointestinal | NMDA | N-methyl-D-aspartic acid | TIA | transient ischemic attack |
| CNS | central nervous system | HR | heart rate | NSTEMI | non-ST elevation myocardial infarction | TCA | tricyclic antidepressant |
| CO | cardiac output | IADL | instrumental activities of daily living | N/V | nausea/ vomiting | UI | urinary incontinence |
| CPR | cardiopulmonary resuscitation | ICU | intensive care unit | OTC | over the counter | UTI | urinary tract infection |

# Physiology and Pathology of Aging

## Definition

- major categories of impairment that develop with old age and affect the physical, mental, and social domains of the elderly, usually due to many predisposing and precipitating factors rather than a single cause

### Table 1. Changes Occurring Frequently with Aging

| System | Physiological Changes | Pathological Changes |
|---|---|---|
| **Neurologic** | Decreased brain mass, cerebral blood flow<br>Increased white matter changes | Increased insomnia, neurodegenerative disease, stroke<br>Decreased reflex response |
| **Senses** | Decreased lacrimal gland secretion, lens transparency, visual acuity, dark adaptation, sense of smell and taste, detection of higher frequency sounds, vestibular function, vestibulospinal reflexes | Increased glaucoma, cataracts, macular degeneration, presbycusis, presbyopia, tinnitus, vertigo, oral dryness |
| **Cardiovascular** | Increased sBP, decreased dBP, HR, CO<br>Decreased baroreflex and autonomic reflexes<br>Decreased vessel elasticity, cardiac myocyte size and number, β-adrenergic responsiveness | Increased atherosclerosis, CAD, MI, CHF, hypertension, arrhythmias, orthostatic hypotension, wide pulse pressure |
| **Respiratory** | Increased tracheal cartilage calcification, mucous gland hypertrophy<br>Decreased elastic recoil, mucociliary clearance, pulmonary function reserve | Increased COPD, pneumonia, pulmonary embolism |
| **Gastrointestinal** | Increased intestinal villous atrophy<br>Decreased esophageal peristalsis, gastric acid secretion, liver mass, hepatic blood flow, calcium and iron absorption | Increased cancer, diverticulitis, constipation, fecal incontinence, hemorrhoids, intestinal obstruction, malnutrition, weight loss |
| **Renal and Urologic** | Increased proteinuria, urinary frequency<br>Decreased renal mass, creatinine clearance, urine acidification, hydroxylation of vitamin D, bladder capacity | Increased urinary incontinence, nocturia, BPH, prostate cancer, pyelonephritis, nephrolithiasis, UTI |
| **Reproductive** | Decreased androgen, estrogen, sperm count, vaginal secretion<br>Decreased ovary, uterus, vagina, breast size | Increased breast and endometrial cancer, cystocele, rectocele, atrophic vaginitis |
| **Endocrine** | Increased NE, PTH, insulin, vasopressin<br>Decreased thyroid and adrenal corticosteroid secretion | Increased DM, hypothyroidism, impaired stress response |
| **Musculoskeletal** | Increased calcium loss from bone<br>Decreased muscle mass, cartilage | Increased arthritis, bursitis, osteoporosis, muscle weakness with gait abnormalities, polymyalgia rheumatica |
| **Integumentary** | Atrophy of sebaceous and sweat glands<br>Decreased epidermal and dermal thickness, dermal vascularity, melanocytes, collagen synthesis | Increased lentigo, cherry hemangiomas, pruritus, seborrheic keratosis, herpes zoster, decubitus ulcers, skin cancer, easy bruising |
| **Psychiatric** | Decreased processing speed, cognitive flexibility, visuospatial perception, working memory and divided attention<br>Loss of synaptic plasticity | Increased depression, dementia, delirium, suicidality, anxiety, sleep disruption |

**Functional Assessment (ADLs and IADLs)**

| ADLs: ABCDE-TT | IADLs: SHAFT-TT |
|---|---|
| **A**mbulating | **S**hopping |
| **B**athing | **H**ousework |
| **C**ontinence | **A**ccounting/Managing finances |
| **D**ressing | **F**ood preparation |
| **E**ating | **T**ransportation |
| **T**ransferring | **T**elephone |
| **T**oileting | **T**aking medications |

Can use formal assessment tools such as the Lawton-Brody Instrumental Activities of Daily Living Scale to assess functioning

**Comprehensive Geriatric Assessment for Older Adults Admitted to Hospital**
Cochrane DB Syst Rev 2017;CD006211
Inpatient comprehensive geriatric assessment increases likelihood that patients will be alive in their own homes at 3-12 mo follow-up (risk ratio (RR) 1.06, 95% confidence interval (CI) 1.01-1.10), decreases the likelihood that patients will be admitted to a nursing home at 3-12 mo (RR 0.80, 95% CI 0.72-0.89), and results in little or no difference in dependence (RR 0.97, 95% CI 0.89-1.04). Evidence for cost-effectiveness is of low-certainty due to imprecision and inconsistency among studies.

# Differential Diagnoses of Common Presentations

## Frailty

### Definition

- frailty: clinically-recognizable state of decreased reserve in older adults with increased vulnerability to acute stressors resulting from functional decline across multiple physiologic systems
- functional decline: progressive limitation in the ability to carry out basic functional activities

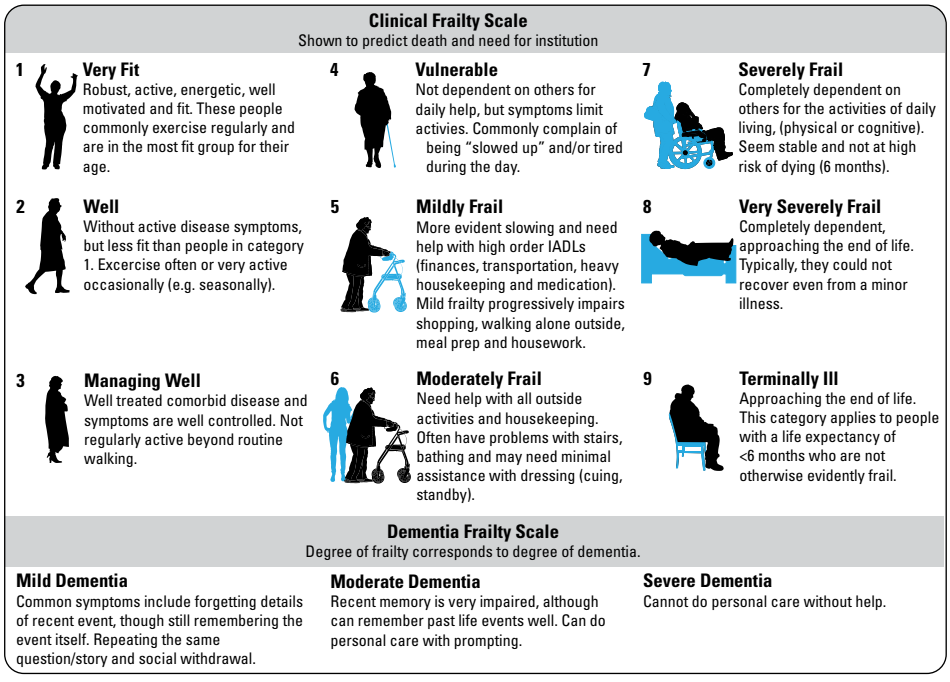



**Figure 1. Frailty scale**

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### Models of Frailty

**Physical Frailty (PF) Phenotype (Fried et al.)**

- **Frail** = 3 or more criteria; at-risk or pre-frail = 1 or 2 criteria
  1. Shrinking: unintentional weight loss (baseline: >10 lbs or 5% total body weight lost in prior year)
  2. Weakness: grip strength in lowest 20% (by gender, BMI)
  3. Poor endurance: as indicated by self-report of exhaustion
  4. Slowness: walking time/15 feet in slowest 20% (by gender, height)
  5. Low activity: kcals/wk in lowest 20% (males: <383 kcals/wk, females: <270 kcals/wk)

**Cumulative Deficit Approach (Rockwood et al.)**

- balance between assets (e.g. health, attitudes, resources, caregiver) and deficits (e.g. illness, disability, dependence, caregiver burden) that determines whether a person can maintain independence in the community
- **Frailty Index** = number of deficits present/number of deficits possible

**Screening Tool for Frailty - FRAIL**
**F**atigue: "Are you fatigued?"
**R**esistance: "By yourself and without aids, do you have any difficulty walking up 10 steps without resting?"
**A**mbulation: "By yourself and without aids, do you have any difficulty walking several hundred yards?"
**I**llnesses: more than five
**L**oss of weight: greater than five percent
Frailty: "Yes" to 3 or more questions
Pre-frailty: "Yes" to 1-2 questions
FRAIL Questionnaire Screening Tool. J Am Med Dir Assoc 2017;18(12):1082-1086.

### Etiology

- multifactorial: dysregulated immune, endocrine, stress, and energy response systems lead to development of clinical frailty

**Table 2. Etiologies of Frailty**

| Etiology | Mechanism |
|---|---|
| **Physiologic Changes with Aging** | Sarcopenia (age-related loss of skeletal muscle and strength), decreased mass and increased stiffness of organs, decreased reserve capacity of systems |
| **Immune System** | Elevated levels of circulating interleukin-6, C-reactive protein, white blood cells, and monocytes associated with skeletal muscle decline<br>Elevated clotting markers (factor VIII, fibrinogen, D-dimer) upregulates clotting cascade<br>Chronic inflammation |
| **Endocrine System** | Decreased skeletal muscle mass via:<br>Decreased growth hormone and IGF-1<br>Increased cortisol levels<br>Decreased DHEA-S<br>Decreased 25 (OH) vitamin D |
| Dysregulated Stress Dysregulation of autonomic nervous system | |
| Age-related changes in renin-angiotensin system and mitochondria likely impact sarcopenia and inflammation | |

### Evidence-based Approach to the Frail Older Patient

- **Comprehensive Geriatric Assessment**
  - includes: Past Medical History, Medications, Allergies, Social History, Function, Physical Exam, and Geriatric Review of Systems (cognition, mood, sleep, pain, nutrition, falls, continence, vision/hearing, skin, and safety)
- interdisciplinary primary care
- pharmaceutical care and medication optimization
- management of geriatric syndromes (e.g. falls, cognitive impairment, incontinence)
- caregiver support

## Delirium

- see Psychiatry, PS22 and Neurology, N20

### Definition

- acute and potentially reversible disturbance in cognition, attention, or level of consciousness
- screened using the Confusion Assessment Method: delirium likely if 1 + 2 and either 3 or 4 are present
  - 1: acute onset and fluctuating course
  - 2: inattention
  - 3: disorganized thinking
  - 4: altered level of consciousness

### Differential Diagnosis

- 3Ds (dementia, delirium, depression) can present with overlapping cognitive changes

### Work-Up

- work-up is not universal, and depends on possible causes based on history and physical exam:
  - Drugs: medication review
  - Infection, Infarction, Inflammation: CBC, urinalysis, urine culture, blood culture, chest x-ray, ECG/troponin
  - Metabolic: basic and extended electrolytes, Vit B12, TSH, LFT, toxicology screen
  - Structural: neurologic exam, CT head

### Delirium Prevention in Elderly

- ensure optimal vision and hearing to support orientation (e.g. appropriate eyewear and hearing aids)
- provide adequate nutrition and hydration (up in chair to eat and drink whenever feasible)
- encourage regular mobilization to build and maintain strength, balance, and endurance
- avoid unnecessary medications and monitor for drug interactions
- avoid bladder catheterization
- ensure adequate sleep at night and wakefulness during the day

**Antipsychotics for Treatment of Delirium in Hospitalised non-ICU Patients**
Cochrane DB Syst Rev 2018;CD005594
**Objectives**: To compare the efficacy and incidence of adverse effects of antipsychotics in the treatment of delirium.
**Selection Criteria**: Types of studies included randomized trials with concealed allocation of subjects.
**Results**: Nine studies with 727 participants testing antipsychotics for delirium treatment; four trials compared an antipsychotic to another drug class or placebo and seven of the nine trials compared a typical antipsychotic to an atypical antipsychotic.
**Conclusions**: There is no evidence that antipsychotics shorten the course of delirium, reduce mortality risks, or improve quality of life in hospitalized patients.

**Table 3. Differentiating the Three Ds of Cognitive Impairment**

| | Dementia | Delirium | Depression |
|---|---|---|---|
| **Onset** | Gradual or step-wise decline | Acute (hours to days) | Subacute (weeks to months) |
| **Duration** | Months to years | Days to weeks | Variable |
| **Natural History** | Progressive, usually irreversible | Fluctuating, reversible<br>High mobidity/mortality in very old | Recurrent, usually reversible |
| **Level of Consciousness** | Normal | Fluctuating | Normal |
| **Attention** | Intact initially | Impaired, difficulty concentrating | |
| **Orientation** | Intact initially | Impaired, fluctuates | Intact |
| **Behaviour** | Disinhibition, loss of ADL/IADLs, personality change | Severe agitation/retardation | Importuning, self-harm/suicide |
| **Psychomotor** | Normal | Fluctuates between extremes | Slowing |
| **Sleep-Wake Cycle** | Fragmented sleep at night | Reversed sleep-wake cycle | Early morning awakening |
| **Mood and Affect** | Labile but not usually anxious | Anxious, irritable, fluctuating | Depressed, stable |
| **Cognition** | Decreased executive function, paucity of thought | Fluctuation preceded by mood changes | Concentration impaired |
| **Memory Loss** | Short-term | Marked short-term | Short-term |

# Falls

## Definition
- an event resulting in a person coming to rest inadvertently on a lower level, other than as a consequence of sudden paralysis, epileptic seizure, or overwhelming external force

## Epidemiology
- 30-40% of people >65 yr old and ~50% of people >80 yr old fall each year
  - equally common between men and women, but more likely to result in injury in women and death in men
  - falls are the leading cause of death from injury in persons ≥65 yr
  - 25% associated with serious injuries (e.g. hip fracture, head injury, bruises, laceration)
  - between 25-75% do not recover to previous level of ADL function after injurious falls

## Etiology
- intrinsic factors
  - age-related changes and diseases associated with aging: musculoskeletal (arthritis, muscle weakness), sensory (visual, proprioceptive, vestibular), cognitive (depression, dementia, delirium, anxiety), cardiovascular (CAD, arrhythmia, MI, low BP), neurologic (stroke, decreased LOC, gait disturbances/ataxia), metabolic (glucose, electrolytes)
  - orthostatic/syncopal
  - acute illness, exacerbation of chronic illness
- extrinsic factors
  - environmental (e.g. home layout, slippery surfaces, overcrowding, new environments)
  - side effects of medications, polypharmacy (>4 medications), and substance abuse (e.g. alcohol)
- situational factors
  - activities (e.g. rushing to the toilet, walking while distracted)

## History and Physical Exam
- history: previous falls and/or gait instability, inquire about intrinsic, extrinsic and situational factors, associated symptoms, loss of consciousness, medication and alcohol use, change in medications
- have a witness present if possible for interview
- physical exam: orthostatic blood pressure, cardiac, visual acuity, examination of feet and footwear, Performance-Oriented Assessment of Mobility, Timed Up-and-Go Test, MSK, neurologic

## Investigations
- comprehensive geriatric assessment to identify all potential causes
- CBC, electrolytes, BUN, creatinine, glucose, $Ca^{2+}$, TSH, B12, urinalysis, cardiac enzymes, ECG, CT head (as directed by history and physical), coagulation profile
- bone densitometry (DEXA) for osteoporosis screening in all women and men >65 yr old

## Interventions
- multidisciplinary, multifactorial, health, and environmental risk factor assessment and intervention programs in the community
- muscle strengthening, balance retraining (e.g. Tai Chi), and group exercise programs
- home hazard assessment and modification (e.g. remove loose rugs and tripping hazards, add shower bars and stair railing, improve lighting)
- prescription of vitamin D 1000 IU daily if vitamin D stores are low
- tapering or gradual discontinuation of psychotropic medication
- postural hypotension, heart rate, and rhythm abnormalities management
- eyesight (cataract surgery) and footwear optimization
- compression socks if venous stasis edema

**Key Clinical History Findings in Falls Evaluation - SPLATT:**
**S**ymptoms
**P**revious falls
**L**ocation of falls
**A**ctivity at the time of fall
**T**ime of fall
**T**rauma

**Will My Patient Fall?**
JAMA 2007;297:77-86
**Purpose**: To identify the prognostic value of risk factors for future falls among older patients.
**Study Selection**: Meta-analysis of prospective cohort studies of risk factors for falls.
**Results**: 18 studies were included. Clinically identifiable risk factors were identified across 6 domains: orthostatic hypotension, visual impairment, impairment of gait or balance, medication use, limitations in basic or instrumental activities of daily living, and cognitive impairment. The estimated pretest probability of falling at least once in any given yr for individuals 65 yr and older was 27% (95% CI 19-36%). Patients who have fallen in the past yr are more likely to fall again (LR2.3-2.8). Best predictors of future falls were disturbances in gait or balance (LR 1.7-2.4), while visual impairment, impaired cognition and medication were not reliable predictors.
**Conclusions**: Screening for risk of falling during the clinical examination begins with determining if the patient has fallen in the past yr. For patients who have not previously fallen, screening consists of an assessment of gait and balance. Patients who have fallen or who have a gait or balance problem are at higher risk of future falls.

**Comparisons of Interventions for Preventing Falls in Older Adults: A Systematic Review and Meta-analysis**
JAMA 2017;318(17):1687-99
**Objective**: To assess the potential effectiveness of interventions for preventing falls.
**Methods**: RCT of fall-prevention interventions for adults ≥65 yr.
**Results/Conclusions**: Exercise alone (OR 0.51, 95% CI 0.33-0.79), exercise + vision assessment/treatment (OR 0.17, 95% CI 0.07-0.38), exercise + vision assessment/treatment + environmental assessment/modification (OR 0.30, 95% 0.13-0.70), and comprehensive geriatric assessment + $Ca^{2+}$ and Vitamin D supplementation (OR 0.12, 95% CI 0.03-0.55) were each associated with lower risk of injurious falls.

**Impact of Medication Classes on Falls Risk in Geriatrics (Odds Ratios)**
- Antidepressants (1.68)
- Neuroleptics/Antipsychotics (1.59)
- Benzodiazepines (1.57)
- Sedatives/ Hypnotics (1.47)
- Antihypertensive agents (1.24)
- NSAIDs (1.21)
- Diuretics (1.07)
- β-blockers (1.01)

Meta-analysis of the impact of 9 medication classes on falls in elderly persons. Arch Intern Med 2009:169(21):1952-60

# Malnutrition

## Definition
- no uniformly accepted definition of malnutrition in older adults. Some commonly used definitions include the following:
  - involuntary weight loss (community: ≥2% over 1 mo, >10 lbs over 6 mo, or ≥4% over 1 yr; nursing home: ≥5% over 1 mo, ≥10% over 180 d)
  - hypoalbuminemia (community: ≤38 g/L; hospital: ≤35 g/L), hypocholesterolemia (<4.1 mmol/L)
  - other features include: insufficient energy intake, loss of muscle mass, fluid accumulation (e.g. edema), loss of subcutaneous fat, decreased hand-grip function

## Etiology
- nutritional
  - decreased assimilation: impaired transit, maldigestion, malabsorption
  - decreased intake: financial, psychiatric (depression), cognitive deficits, anorexia associated with chronic disease, functional deficits (e.g. difficulty shopping, preparing meals or feeding oneself due to functional impairment)

- stress: acute or chronic illness/infection, chronic inflammation, abdominal pain
- mechanical: dental problems, dysphagia
- age-related changes: appetite dysregulation, decreased thirst
- mixed: increased energy demands (e.g. hyperthyroidism), abnormal metabolism, protein-losing enteropathy

### Clinical Features
- history
  - weight loss in 6 mo prior to examination
  - recent or chronic illness
  - constitutional symptoms (e.g. recent weight loss)
  - dietary intake in relation to usual pattern
  - depression, GI symptoms (anorexia, nausea, vomiting, diarrhea)
  - functional disability: impaired ADLs and IADLs
  - social factors: economic barriers, dental problems, and living situation (e.g. living alone)
- physical exam
  - BMI <23.5 in males, <22 in females should raise concern
  - muscle wasting, temporal wasting, presence of triceps skin fold
  - loss of subcutaneous fat
  - ankle or sacral edema, ascites
  - assess cognition

### Investigations
- CBC, electrolytes, $Ca^{2+}$/albumin, $Mg^{2+}$, $PO_4^{3-}$, creatinine, LFTs (INR, bilirubin), B12, folate, TSH, lipid profile
- if indicated by assessment, can consider urinalysis, ESR, CXR

### Treatment
- direct treatment at underlying causes
- dietary modification: high calorie foods, oral nutritional supplementation: patient specific meal replacement products (e.g. Ensure™, Glucerna™, Nepro™), vitamins/minerals (e.g. B12, calcium, vitamin D)
- referral: speech language pathologist, nutritionist

**Etiology of Malnutrition in the Elderly**

**MEALS ON WHEELS**
**M**edications
**E**motional problems
**A**norexia
**L**ate-life paranoia
**S**wallowing disorders
**O**ral problems
**N**osocomial infections
**W**andering/dementia related activity
**H**yperthyroid/Hypercalcemia/Hypoadrenalism
**E**nteric disorders
**E**ating problems
**L**ow-salt/Low-fat diet
**S**tones

## Constipation

- see Gastroenterology, G27

### Definition
- Rome IV Diagnostic Criteria: straining, hard stools, sensation of incomplete evacuation, use of digital maneuvers, and/or sensation of anorectal obstruction/blockage with 25% of bowel movements and <3 bowel movements per wk. The criteria must be fulfilled for the last 3 mo with symptom onset ≥ 6 mo prior to diagnosis

### Epidemiology
- chronic constipation increases with age (up to 1/3 of patients >65 yr experience constipation and 1/2 of patients >80 yr)
- in the elderly, chronic constipation may present as fecal impaction

### Pathophysiology
- impaired rectal sensation (increased rectal distention required to stimulate the urge to defecate)
- colorectal dysmotility

### Treatment
- non-pharmacological
  - increase fibre intake (note: bulking agents, e.g. psyllium, Metamucil, may worsen constipation)
  - ensure adequate fluid intake
  - increase physical activity
- pharmacological
  - discourage chronic laxative use
  - review medication regime, reduce dosages or substitute
- see *Common Medications*, GM14

**Common Causes of Constipation in the Geriatric Population include:**
- Primary impaired colonic and anorectal function
- Drugs (see below)
- Diet (dehydration, low fibre "tea and toast" diet)
- Colo-anorectal disorders (cancer, masses, stenosis, strictures)
- Neurologic (stroke, dementia, Parkinson's, autonomic neuropathy)
- Psychiatric (depression, anxiety)

**Drugs Associated with Constipation include:**
- OTC (antihistamines, NSAIDs)
- Opioids
- Psychotropic (antipsychotics, TCAs)
- Anticholinergics
- Calcium channel blockers
- Diuretics
- Supplements (iron or calcium)

Diagnostic approach to chronic constipation in adults. Am Fam Physician 2011;84:299-306

**Treatment of Constipation in Older Adults**
Can Med Assoc J 2013;185(8):663-70
**Objectives**: To discuss management of constipation in older adults.
**Results/Conclusions**: In older adults, the predominant symptom of constipation is more frequently straining than decreased stool frequency. RCTs support the use of osmotic agents to treat symptoms of constipation in older adults. In contrast, evidence supporting the use of bulk agents, stool softeners stimulants, and prokinetic agents is lacking, limited, and inconsistent.

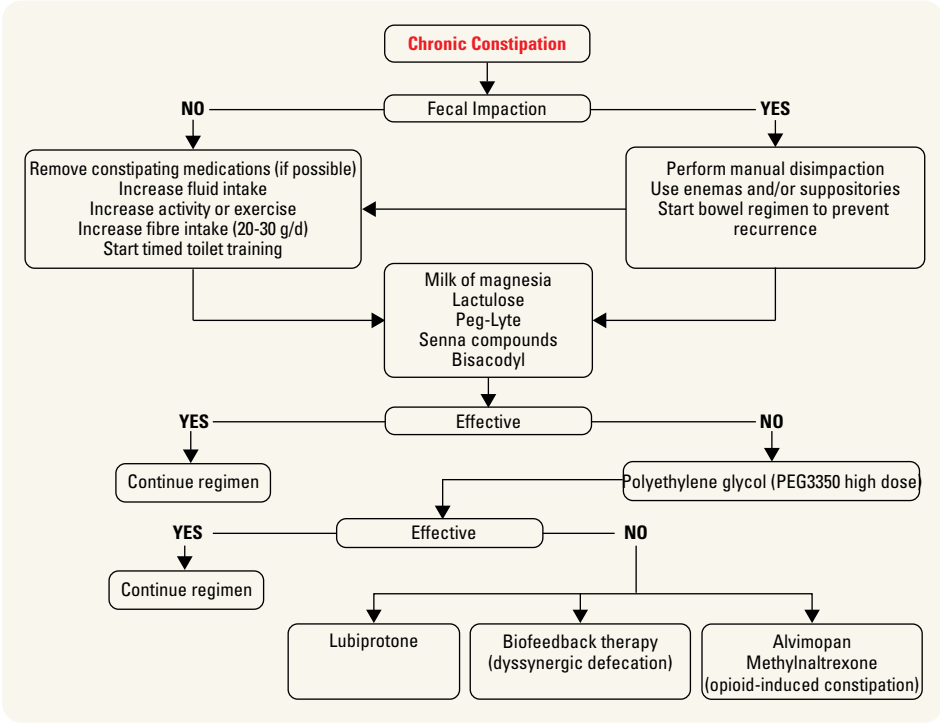



**Figure 2. Treatment algorithm for the management of chronic constipation in the elderly**
Adapted from: Clin Interv Aging 2010;5:163-171

# Incontinence

## FECAL INCONTINENCE

### Definition
- involuntary or inappropriate passing of feces that impacts social functioning or hygiene
- severity can range from unintentional flatus to the complete evacuation of bowel contents
- there are three subtypes:
  1. passive incontinence: involuntary discharge of stool or gas without awareness
  2. urge incontinence: discharge of fecal matter in spite of active attempts to retain bowel contents
  3. fecal seepage: leakage of stool following otherwise normal evacuation

**Transient Causes of Incontinence**

**DIAPERS**
**D**elirium
**I**nfection
**A**trophic urethritis/vaginitis
**P**harmaceuticals
**E**xcessive urine output
**R**estricted mobility
**S**tool impaction

### Epidemiology
- the incidence of fecal incontinence differs by setting: community (17-36%), hospital (16%) and nursing home (33-65%)
- risk factors: constipation, age >80 yr, female sex, urinary incontinence, impaired mobility, dementia, neurologic disease

### Etiology
- physiological changes with age >80 yr (e.g. decreased external sphincter strength, decreased resting tone of internal sphincter, weakened anal squeeze, increased rectal compliance, and impaired anal sensation)
- trauma (e.g. vaginal delivery, pudendal nerve damage, cauda equina)
- iatrogenic
  - surgical (e.g. anorectal surgery, lateral internal sphincterotomy, hemorrhoidectomy, colorectal resection)
  - radiation (e.g. pelvic radiation)
- neurogenic (e.g. neuropathy, stroke, MS, diabetic neuropathy)
- anorectal/colorectal diseases (e.g. rectal prolapse, hemorrhoids, IBD, rectocele, cancer)
- medication (e.g. laxative, anticholinergics, antidepressants, caffeine, muscle relaxants)
- cognitive (e.g. dementia, willful soiling with psychosis)
- constipation/fecal impaction

### Investigations (if cause not apparent from history and physical)
- differentiate true incontinence from frequency and urgency (e.g. IBS, IBD)
- stool studies
- endorectal ultrasound
- colonoscopy, sigmoidoscopy, anoscopy
- anorectal manometry/functional testing

### Management
- physiological changes with age: medication management (anti-motility agents (e.g. loperamide), diet/bulking agents for loose stool) increase fluid intake, biofeedback, retraining of pelvic floor muscles, surgery
- trauma: direct surgical repair or augmentation of the sphincters
- iatrogenic: surgical repair, artificial sphincters
- neurogenic: medication management, abdominal massage, digital stimulation for dysfunction, biofeedback and behavioural training, prevent autonomic dysreflexia in spinal injury
- anorectal/colorectal diseases: treat underlying cause (optimize IBD medications), surgical (e.g. mass removal, prolapse repair, hemorrhoid removal, colostomy)
- medication-related causes: stop laxatives, lower dose or discontinue any other offending agents
- cognitive: regular defecation program in patients with dementia, psychiatric consult (optimize medications and cognitive function)
- constipation/fecal impaction: disimpaction, prevent impaction, enema or rectal irrigation

## URINARY INCONTINENCE
- see Urology, U6

### Definition
- complaint of any involuntary loss of urine
- there are 4 subtypes:
  1. stress incontinence: leakage associated with physical strain
  2. urge incontinence: leakage associated with strong urge to urinate
  3. overflow incontinence: leakage associated with poor bladder emptying
  4. functional incontinence: leakage due to illness or disability not related to the urinary tract

### Epidemiology
- 15-30% prevalence dwelling in community and at least 50% of institutionalized seniors
- morbidity: cellulitis, pressure ulcers, urinary tract infections, falls with fractures, sleep deprivation, social withdrawal, depression, sexual dysfunction
- not associated with increased mortality
- risk factors: impaired mobility, falls, medications, depression, TIA/stroke, dementia, CHF, obesity

### Etiology
- physiologic changes with age: decreased bladder capacity
- genitourinary diseases (e.g. cystitis, urethritis, benign prostatic hyperplasia)
- neurogenic (e.g. cauda equina syndrome, stroke, MS)
- iatrogenic: prostate surgery
- trauma: pelvic trauma, traumatic spinal cord injury
- drugs (e.g. alcohol, loop diuretics, sedative hypnotics, GABAergic agents)
- cognitive (e.g. dementia, depression)
- functional impairment (e.g. arthritis, poor vision)

### Investigations
- urinalysis and culture

### Management
- lifestyle modification: avoid excessive fluid intake and alcohol
- pharmacologic: **β**-adrenergic agonists to reduce involuntary bladder contractions
- physiologic changes with age: pelvic muscle exercises, bladder training, biofeedback
- genitourinary diseases: treat underlying cause (empiric antimicrobial treatment for cystitis, **α** blockers/5-**α** reductase inhibitors for benign prostatic hyperplasia)
- functional impairment: incontinence pads, environmental modification, personal assistance
- cognitive: referral to incontinence program if needed

# Immobility

### Complications
- cardiovascular: orthostatic hypotension, venous thrombosis, embolism
- respiratory: decreased ventilation, atelectasis, pneumonia
- gastrointestinal: anorexia, constipation, incontinence, dehydration, malnutrition
- genitourinary: infection, urinary retention, bladder calculi, incontinence
- musculoskeletal: atrophy, contractures, bone loss
- skin: pressure ulcers
- psychological: sensory deprivation, delirium, depression

# Pressure Ulcers

• see Plastic Surgery, PL17

## Definition

• any lesion caused by unrelieved pressure resulting in damage of underlying tissue; usually develops over bony prominences

## Risk Factors

• extrinsic: friction, pressure, shear force
• intrinsic: immobility, malnutrition, moisture, sensory loss
• geriatric: age related skin changes, bed-bound, cognitive impairment, chronic illness, use of anti-hypertensive medications

**Table 4. Classification of Pressure Ulcers**

| | |
|---|---|
| **Stage I** | Changes include skin temperature, tissue consistency or sensation |
| | An area of persistent erythema in lightly pigmented, intact skin; in darker skin, it may appear red, blue or purple |
| **Stage II** | Partial thickness skin loss involving the epidermis, dermis or both |
| | The ulcer is superficial and presents as an abrasion, blister or shallow crater |
| **Stage III** | Full thickness skin loss involving damage or necrosis of subcutaneous tissue which may extend down to, but not through, underlying fascia |
| | Presents as a deep crater with or without undermining of adjacent tissue |
| **Stage IV** | Full thickness skin loss with extensive destruction, tissue necrosis or damage to muscle, bone or supporting structures |
| | May have associated undermining and/or sinus tracts |

## Prevention

• pressure reduction
  ▪ frequent repositioning
  ▪ pressure-reducing devices (static, dynamic)
• maintaining nutrition, encouraging mobility and managing incontinence
• use validated pressure injury risk assessment tools on admission for those identified to be at risk for skin breakdown (Canadian Association of Wound Care, 2018)

## Treatment

• optimize nutritional status
• minimize pressure on wound
• analgesia
• all ulcers with necrosis warrant debridement (mechanical, enzymatic and autolytic are non-urgent forms of debridement, whereas sharp debridement is performed urgently due to risk for sepsis or cellulitis)
• dressing application (exudate absorbing, barrier products to reduce friction)
• maintain moist wound environment to enable re-epithelialization
• treatment of wound infections (topical gentamicin, silver sulfadiazine, mupirocin)
• diabetic foot ulcers: offloading with removable cast walker (e.g. aircast boot), orthopedic shoes and orthotics
• swab wounds not demonstrating clinical improvement for C&S; biopsy chronic wounds to rule out malignancy
• referral to Wound Care
• consider other treatment options
  ▪ negative pressure wound therapy/vacuum-assisted closure
  ▪ biological agents: application of fibroblast growth factor, platelet-derived growth factor to wound
  ▪ non-contact normothermic wound therapy
  ▪ electrotherapy



**Risk Assessment and Prevention of Pressure Ulcers**
Ann Intern Med 2015;162:359-369
The American College of Physicians (ACP) strongly recommends advanced static mattresses or advanced static overlays for patients who are at an increased risk of developing pressure ulcers. The ACP also recommends against using alternating air-mattresses or alternating-air overlays.

# Hazards of Hospitalization

**Table 5. Recommendations for Sequelae of Hospitalization in Older Patients**

| Sequelae | Recommendations |
|---|---|
| **Malnutrition** | No dietary restrictions (except diabetes), assistance, dentures if necessary, sitting in a chair to eat |
| **Urinary Incontinence** | Medication review, remove environmental barriers, discontinue use of catheter |
| **Depression** | Routine screening |
| **Adverse Drug Event** | Medication review |
| **Confusion/Delirium** | Orientation, visual and hearing aids, volume repletion, noise reduction, early mobilization, medication review, remove restraints |
| **Pressure Ulcers** | Low-resistance mattress, daily inspection, repositioning every 2 h |
| **Infection** | Early mobilization, remove unnecessary IV lines, catheters, NG tubes |
| **Falls** | Appropriate footwear, assistive devices, early mobilization, remove restraints, medication review |
| **Hypotension/Dehydration** | Early recognition and repletion (ideally oral rehydration, if possible) |
| **Diminished Aerobic Capacity/ Loss of Muscle Strength/ Contractures** | Early mobilization |
| **Decreased Respiratory Function** | Incentive spirometry, physiotherapy |
| **Functional Decline** | Structured exercise, progressive resistance training, walking programs |

Source: Asher, Richard AJ. Dangers of going to bed. British Medical Journal 2.4536 (1947): 967

# Elder Abuse

## Definition

- includes physical abuse, sexual abuse, emotional/psychological abuse, financial exploitation and neglect
- elder abuse is a criminal offence under the Criminal Code of Canada and in most U.S. states

## Epidemiology

- in Canada in 2013, almost 3000 seniors were victims of family violence. The perpetrators of family violence against seniors were identified to be their grown child (43% of cases) and their spouses (28% of the cases)
- in older adults aged ≥60 yr, elder abuse is estimated to occur in 10% of patients
- insufficient evidence to include/exclude screening in the Periodic Health Exam

## Risk Factors

**Table 6. Risk Factors for Elder Abuse**

| | |
|---|---|
| **Situational Factors** | Social |
| **Victim Characteristics** | Physical or emotional dependence on caregiver<br>Lack of close family ties<br>History of family violence<br>Dementia or recent deterioration in health |
| **Perpetrator Characteristics** | Related to victim<br>Dependency on older adult (e.g. financial dependency) |

# Presbycusis

- see Otolaryngology, OT19

# Driving Competency

## Reporting Requirements

- physician-reporting to the Ministry of Transportation is mandatory in all provinces and territories except in Quebec, Nova Scotia, and Alberta, where it is discretionary
- British Columbia, Ontario: must refer for re-test at ≥80 yr
- not an issue unique to geriatrics – any patient may suffer from a medical condition that impairs their ability to drive and should be reported
- in the U.S., varies by state

## Conditions that may Impair Driving

**Table 7. Conditions that Impair Driving**

| | |
|---|---|
| **Alcohol** | Patients with history of impaired driving and those with a high probability of future impaired driving should not drive until further assessed |
| | Alcohol dependence or abuse: if suspected, should be advised not to drive |
| | Alcohol withdrawal seizure: must complete a rehabilitation program and remain abstinent and seizure-free for 6 mo before driving |
| **Blood Pressure Abnormalities** | Hypertension: sustained BP >170/110 should be evaluated carefully |
| | Hypotension: sustained BP <90/60; if syncopal, discontinue driving until syncope is treated and preventable |
| **Cardiovascular Disease** | Suspected asymptomatic CAD or stable angina: no restrictions |
| | STEMI, NSTEMI with significant LV damage, coronary artery bypass surgery: no driving for 1 mo following hospital discharge |
| | NSTEMI with minor LV damage, unstable angina: no driving for 48 h if PCI or 7 d if no PCI performed |
| **Cerebrovascular Conditions** | TIA: should not be allowed to drive until a medical assessment is completed |
| | Stroke: should not drive for at least 1 mo; may resume driving if functionally able; no clinically significant motor, cognitive, perceptual or vision deficits; no obvious risk of sudden recurrence; underlying cause appropriately treated; no post-stroke seizure |
| **COPD** | Mild/moderate impairment: no restrictions |
| | Moderate or severe impairment requiring supplemental oxygen: road test with supplemental oxygen |
| **Cognitive Impairment/ Dementia** | Moderate to severe dementia is a contraindication to driving; defined as the "inability to independently perform 2 or more IADLs or any basic ADL" |
| | Patients with mild dementia should be assessed; if indicated, refer to specialized driving testing centre; if deemed fit to drive, re-evaluate patient every 6-12 mo |
| | Poor performance on MMSE, clock drawing or Trails B suggests a need to investigate driving ability further |
| | MMSE score alone (whether normal or low) is insufficient to determine fitness to drive |
| **Diabetes** | Diet controlled or oral hypoglycemic agents: no restrictions in absence of diabetes complications that may impair ability to drive (e.g. retinopathy, nephropathy, neuropathy, cardiovascular or cerebrovascular disease) |
| | Insulin use: may drive if no complications (as above) and no severe hypoglycemic episode in the last 6 mo |
| **Drugs** | Be aware of: analgesics, anticholinergics, anticonvulsants, antidepressants, antipsychotics, opiates, sedatives, stimulants |
| | Degree of impairment varies: patients should be warned of the medication/withdrawal effect on driving |
| **Hearing Loss** | Effect of impaired hearing on ability to drive safely is controversial |
| | Acute labyrinthitis, positional vertigo with horizontal head movement, recurrent vertigo: advise not to drive until condition resolves |
| **Musculoskeletal Disorders** | Physician's role is to report etiology, prognosis and extent of disability (pain, range of motion, coordination, muscle strength) |
| **Post-Operative** | Outpatient, conscious sedation: no driving for 24 h |
| | Outpatient, general anesthesia: no driving for ≥24 h |
| **Seizures** | First, single, unprovoked: no driving for 3 mo until complete neurologic assessment, EEG, CT head |
| | Epilepsy: can drive if seizure-free on medication and physician has insight into patient compliance |
| **Sleep Disorders** | If patient is believed to be at risk due to a symptomatic sleep disorder but refuses investigation with a sleep study or refuses appropriate treatment, the patient should not drive |
| **Visual Impairment** | Visual acuity: contraindicated to drive if <20/50 with both eyes examined simultaneously |
| | Visual field: contraindicated to drive if <120° along horizontal meridian and 15° continuous above and below fixation with both eyes examined simultaneously |

N.B. guidelines included refer specifically to private driving; please see CMA guidelines for commercial driving





**Key Factors to Consider in Older Drivers**
**SAFEDRIVE**
**S**afety record
**A**ttention (e.g. concentration lapses, episodes of disorientation)
**F**amily observations
**E**thanol abuse
**D**rugs
**R**eaction time
**I**ntellectual impairment
**V**ision/**V**isuospatial function
**E**xecutive functions (e.g. planning, decision-making, self-monitoring behaviours)
Geriatrics 1996;51:36-45



**Cognitive Tests and Determining Fitness to Drive in Dementia: A Systematic Review**
J Am Geriatr Soc 2016;64(9):1904-17
**Objectives**: To examine the relationship between cognitive tests and driving to determine whether a cognitive assessment can be implemented as a tool to examine driver safety.
**Methods**: Systematic review of 28 studies investigating the relationship between cognitive functioning and driving in individuals with dementia.
**Results**: Composite batteries comprising multiple individual tests from different cognitive domains consistency predicted driving performance for individuals with dementia. Scores on individual tests or tests of a single cognitive domain did not predict driver safety.
**Conclusions**: While studies consistently found composite batteries predicted driving performance, these tests were not clinically usable as they lacked the ability to discriminate between safe and unsafe drivers. Need development of a reliable, valid composite battery that can correctly determine driver safety in patients with dementia.

# Health Care Institutions

**Table 8. Classification of Health Care Services and Institutions**

| Institution/Service | Description |
|---|---|
| **Community Support Services** | Health care services offered at home for those who can live independently at home or under the care of family members including professional health care services, personal care and support (ADL assistance), homemaking (IADL assistance), community support services (e.g. transportation, meal delivery, day programs, caregiver relief, security checks, etc.) |
| **Rehabilitation** | Health care services offered in an institution to optimize patients' function, independence and quality of life |
| **Residential** | Divided into short (<60-90 d/yr) and long (indefinite) stay |
| **a) Seniors Affordable Housing** | Seniors who live independently and manage their own care, but prefer to live near other seniors; usually has accessibility features; rent is adjusted based on income |
| **b) Retirement Home** | Residents are fairly independent and require minimal support with ADLs and IADLs; often privately owned |
| **c) Supportive Housing** | Residents require minimal to moderate assistance with daily activities while living independently; often rental units in an apartment; may offer physiotherapy and rehabilitation services |
| **d) Long-term Care/Skilled Nursing Facility** | Around the clock nursing care and on-call physician coverage; often offers occupational therapy, physiotherapy, respiratory therapy, and rehabilitation services; may be used short-term for caregiver respite or for supportive patient care to regain strength and confidence after leaving the hospital |
| **e) Hospice** | Free-standing facility or designated floor in a hospital or nursing home for care of terminally ill patients and their families; focus is on quality of life and often requires prognosis ≤3 mo |

- names of community health care institutions, types of facilities, and services offered vary between geographical locations
- factors to consider when seeking services/institutions: level of care required, support networks, duration of stay, cost

# Geriatric Pharmacology

## Pharmacokinetics

**Table 9. Age-Associated Pharmacokinetics**

| Parameter | Age Effect | Implications |
|---|---|---|
| **Absorption** (less significant) | Increased gastric pH<br>Decreased splanchnic blood flow, GI absorptive surface and dermal vascularity; delayed gastric emptying | Drug-drug and drug-food interactions are more likely to affect absorption |
| **Distribution** | Increased total body fat<br>Increased α1-glycoprotein<br>Decreased lean body mass and total body water<br>Decreased albumin | Lipophilic drugs have a larger volume of distribution<br>Increased binding of basic drugs<br>Decreased volume of distribution of hydrophilic drugs<br>Decreased binding of acidic drugs |
| **Metabolism** (less significant) | Decreased hepatic mass and hepatic blood flow; impaired phase I reactions (oxidative system) | Lower doses may be therapeutic |
| **Elimination** | Decreased renal blood flow, glomerular filtration rate, tubular secretion<br>Overall reduction in renal function by 30-50% | Lower doses may be therapeutic |

## Pharmacodynamics

### Drug Sensitivity
- changes in pharmacokinetics as well as intrinsic sensitivity lead to altered drug responses
- increased sensitivity to warfarin, sedatives, antipsychotics, anticholinergics, digoxin, and narcotics
- decreased sensitivity to β-blockers and β-adrenergic stimulants, though may have increased sensitivity

### Decreased Homeostasis
- poorer compensatory mechanisms leading to more adverse reactions (e.g. bleeding with NSAIDs/anticoagulants, altered mental status with anticholinergic/sympathomimetic/anti-Parkinsonian drugs)



New medications: Start Low, Go Slow! Avoid starting 2 drugs at the same time



Adverse drug reactions in the elderly may present as delirium, falls, fractures, urinary incontinence/retention or fecal incontinence/impaction

# Polypharmacy

### Definition
- prescription, administration or use of more medications than are clinically indicated

### Epidemiology
- in Canada, >60% of elderly individuals reported using ≥5 medications
- hospitalized elderly are given an average of 10 medications during admission

### Risk Factors for Non-Compliance
- greater number of medications (compliance with 1 medication is 80%, but drops to 25% with ≥6 medications)
- increased dosing frequency, complicated container design, financial constraints, and cognitive impairment

### Adverse Drug Reactions (ADRs)
- any noxious or unintended response to a drug that occurs at doses used for prophylaxis or therapy
- risk factors in the elderly
  - intrinsic: comorbidities (>5), age >85, low BMI, age-related changes in pharmacokinetics and pharmacodynamics, CrCl <50 mL/min
  - extrinsic: number of medications, (>9 medications, >12 doses/d), multiple prescribers, unreliable drug history, prior ADR
- prescribing cascade: process whereby an ADR is misinterpreted as a new medical condition, and a subsequent drug is prescribed to treat the initial drug-induced event. Providers should ask themselves:
  - is the new drug being prescribed to address an adverse event from a previously prescribed drug therapy?
  - is the initial drug therapy potentially leading to a prescribing cascade really needed?
  - what are the harms and benefits of continuing the initial drug therapy?

### Preventing Polypharmacy
- consider drug: safer side effect profiles, convenient dosing schedules, convenient route, efficacy
- consider patient: other medications, clinical indications, medical comorbidities
- consider patient-drug interaction risk factors for ADRs
- review drug list regularly to eliminate medications with no clinical indication or with evidence of toxicity
- avoid treating an ADR with another medication

# Inappropriate Prescribing in the Elderly

### Epidemiology
- the estimated prevalence of potentially inappropriate prescribing ranges from 12-40%

### Beers Criteria
- a list of medications to avoid in adults ≥65 yr due to safety concerns
- 2015 update lists drugs that should be avoided or dose-adjusted based on kidney function, as well as drug-drug interactions associated with harms in older adults
- examples include long-acting benzodiazepines, strong anticholinergics, high-dose sedatives
- the elderly are often under-treated (ACEI, ASA, β-blockers, thrombolytics, oral anticoagulants)

### STOPP/START Criteria
- another screening tool for potentially inappropriate prescribing in the elderly
  - STOPP: Screening Tool of Older Person's Prescriptions
    - systems-based list of medications contraindicated in adults ≥65 in the context of their diagnoses
  - START: Screening Tool to Alert doctors to Right Treatment
    - systems-based list of medications indicated in adults ≥65 in the context of their diagnoses



**Principles for Prescribing in the Elderly**

**CARED**
**C**aution/Compliance
**A**ge (adjust dosage for age)
**R**eview regimen regularly
**E**ducate
**D**iscontinue unnecessary medications
Geriatric Pearls. Philadelphia: FA Davis Company, 1999

# Common Medications

**Table 10. Common Medications**

| Drug Name | Brand Name | Dosing Schedule | Indications | Contraindications | Side Effects | Mechanism of Action |
|---|---|---|---|---|---|---|
| **Cognitive Enhancers** | | | | | | |
| **donepezil** | Aricept® | 5-10 mg PO daily | Moderate to severe dementia of Alzheimer's type | Known hypersensitivity, caution in untreated obstructive airways disease, cardiac conduction abnormalities, active PUD, seizure disorder, syncope NYD | N/V, diarrhea, anorexia, falls, hip fracture, increased need for pacemaker insertion | Reversible inhibition of acetylcholinesterase |
| **galantamine** | Reminyl® | 8-12 mg PO bid | Mild to moderate dementia of Alzheimer's type | Known hypersensitivity, caution in untreated obstructive airways disease, cardiac conduction abnormalities, active PUD, seizure disorder, syncope NYD | N/V, diarrhea, anorexia, falls, hip fracture, increased need for pacemaker insertion | Reversible inhibition of acetylcholinesterase |
| **rivastigmine** | Exelon® | 1.5 mg PO daily (starting) up to 6 mg PO bid | Mild to moderate dementia of Alzheimer's type | Known hypersensitivity, severe hepatic disease, caution in untreated obstructive airways disease, cardiac conduction abnormalities, active PUD, seizure disorder, syncope NYD | N/V, diarrhea, anorexia, falls, hip fracture, increased need for pacemaker insertion | Acetylcholinesterase inhibition (reversible but very slow) |
| **memantine** | Ebixa®/Namenda® (Can)/(U.S.) | 5 mg PO daily (starting) up to 10 mg PO bid | Mild to moderate dementia of Alzheimer's type | Known hypersensitivity, conditions that alkalinize urine, caution in renal failure, seizures | Agitation, fatigue, dizziness, headache, hypertension, constipation | NMDA-receptor antagonist |
| **Laxatives** | | | | | | |
| **bran** | All-Bran® | 1 cup OD | Constipation | | Bloating, flatus | Bulk-forming laxative |
| **psyllium** | Metamucil® Prodiem Plain® | 1 tsp PO tid | Constipation, hypercholesterolemia | N/V, abdominal pain, obstruction | Bloating, flatus | Bulk-forming laxative |
| **lactulose** | Chronulac® Cephulac® Kristalose®(U.S.) Acilac; Apo-Lactulose®; Laxilose; PMS-Lactulose (Can) | 15-30 cc PO OD/bid | Constipation, hepatic encephalopathy, bowel evacuation following barium exam | Patients on low galactose diets Abdominal pain, N/V | Flatus, cramps, nausea, diarrhea | Hyperosmolar agent, lowers pH of colon to decrease blood ammonia levels |
| **senna** | Senokot®/Ex-lax® Glysennid® | 1-2 tabs PO daily or 10-15 cc syrup PO daily | Constipation | Abdominal pain, N/V | Cramps, N/V , diarrhea | Stimulant laxative |
| **PEG 3350 (polyethylene glycol)** | Lax-A-Day®, RestoraLAX®, Pegalax® (Can) Gavilax®, Healthylax® (U.S.) | 17 g (~1 heaping tablespoon) dissolved in 120 to 240 mL (4 to 8 ounces) of beverage, OD | Constipation, bowel prep (different dosing schedule) | Known/suspected bowel obstruction, known hypersensitivity, renal impairment | Abdominal cramps, bloating of the stomach, diarrhea, flatulence, nausea | Osmotic laxative |
| **bisacodyl** | Dulcolax® | 5-15 mg PO (10 mg PR) | Constipation | Ileus, obstruction, abdominal pain, N/V, severe dehydration | Cramps, pain, diarrhea | Stimulant laxative |
| **Parkinsonian Agents** – see Neurology, N32 | | | | | | |

Note: Docusate has been shown to be ineffective for the prevention/treatment of constipation in the elderly

# Landmark Geriatric Trials

| Trial | Reference | Results |
|---|---|---|
| Delirium in Older Persons: Advances in Diagnosis and Treatment | JAMA 2017; 318(12):1161-1174 | Advances in diagnosis can improve recognition and risk stratification of delirium. Prevention of delirium using nonpharmacologic approaches is effective, while pharmacologic prevention and treatment of delirium remains controversial |
| Assessment and management of falls in older people | Can Med Assoc J 2014;186(16):E610-21 | Targeted history and physical examination, covering potential home hazards, cognitive and visual impairment, functional limitations, medications, orthostatic hypotension, and gait and balance abnormalities, can be used to identify risk factors for falls. Numerous interventions (single and multicomponent) can decrease the risk of falls. At a minimum, patients who have experienced a fall should be encouraged to participate in an approved exercise program to help prevent further falls |
| Dementia prevention, intervention, and care | Lancet 2017; 390(10113): 2673-2734 | Recommend active treatment of hypertension in middle aged (45–65 yr) and older people (aged older than 65 yr) without dementia to reduce dementia incidence. Interventions for other risk factors including more childhood education, exercise, maintaining social engagement, reducing smoking, and management of hearing loss, depression, diabetes, and obesity could delay or prevent a third of dementia cases |
| Optimal management of urinary tract infections in older people | Clin Interv Aging 2011;6:173-180 | UTIs are over diagnosed and over treated in older people. Asymptomatic bacteriuria is very common in later life and should not be screened for or treated |
| Delirium is a strong risk factor for dementia in the oldest-old: a population-based cohort study | Brain 2012;135(9): 2809-16 | First population study to show that delirium is a strong risk factor for dementia and cognitive decline in elderly patients |
| Donepezil and Memantine for Moderate-to-Severe Alzheimer's Disease | New Engl J Med 2012;366:893-903 | Continued treatment with donepezil was associated with cognitive benefits over the course of 12 mo in patients with moderate or severe Alzheimer's disease |
| Hip protectors for fracture prevention | New Engl J Med 2000;343:1506-1513 | The risk of hip fracture can be reduced in frail elderly adults by the use of an anatomically designed external hip protector |
| HYVET | New Engl J Med 2008;358:1887-1898 | Antihypertensive treatment with indapamide (sustained release), with or without perindopril, in adults 80 yr or older is beneficial |
| PROFET | Lancet 1999;353:93-97 | Demonstrates that an interdisciplinary approach to elderly adults with a previous history of falls can significantly decrease the risk of further falls and limit functional impairment |
| Reduction of inappropriate benzodiazepine prescriptions through patient education: the EMPOWER cluster randomized trial | JAMA Intern Med 2014;174:890-898 | Direct-to-consumer education describing the risks of benzodiazepine use and a stepwise tapering protocol effectively elicits shared decision making and discontinuation of medications that increase the risk of harm in older adults |
| Updated Beers Criteria for potentially inappropriate medication use in older adults | J Am Geriatr Soc 2015;63:2227-46 | A 13-member interdisciplinary panel of experts in geriatric care and pharmacotherapy updated the 2012 AGS Beers Criteria for medications to be avoided or dose-adjusted in older adults |
| STOPP and START. Consensus validation | Int J Clin Pharmacol Ther 2008;46:72-83 | STOPP/START is a valid, reliable, and comprehensive screening tool that enables the prescribing physician to appraise an older patient's prescription drugs in the context of his/her concurrent diagnoses |
| Frailty in older adults: evidence for a phenotype | J Gerontol A Biol Sci Med Sci 56:M146-56 | This study provides a potential standardized definition of frailty in community-dwelling older adults, where three or more of the following criteria are present: unintentional weight loss, exhaustion, weakness, slow walking speed, and low physical activity |
| Tube feeding in patients with advanced dementia: A review of the evidence | JAMA 1999;282:1365-1370 | There is no direct data to support tube feeding of demented patients with eating difficulties for any of the commonly cited indications. Survival has not been shown to be prolonged by tube feeding |
| Systolic Hypertension in the Elderly Program (SHEP): antihypertensive efficacy of chlorthalidone | Am J Cardiol 1985;56:913-20 | Chlorthalidone is effective for lowering blood pressure in elderly patients with systolic hypertension |
| Systolic Hypertension in Europe (Syst-Eur) trial | Lancet 1997;350:757-64 | Among elderly patients with isolated systolic hypertension, antihypertensive drug treatment starting with nitrendipine reduces the rate of cardiovascular complications. Treatment of 1000 patients for 5 years with this type of regimen may prevent 29 strokes or 53 major cardiovascular endpoints |

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# GY Gynecology

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# Acronyms

| | |
|---|---|
| β-hCG | beta-human chorionic gonadotropin |
| ACEI | angiotensin converting enzyme inhibitors |
| AFP | alpha-fetoprotein |
| AIS | androgen insensitivity syndrome |
| ARB | angiotensin II receptor blockers |
| ASCUS | atypical squamous cells of undetermined significance |
| AUB | abnormal uterine bleeding |
| BMD | Bone mineral density |
| BMI | body mass index |
| BSO | bilateral salpingo-oophorectomy |
| BV | bacterial vaginosis |
| CAH | congenital adrenal hyperplasia |
| CHC | combined hormonal contraception |
| CMV | cytomegalovirus |
| D&C | dilatation and curettage |
| DES | diethylstilbestrol |
| DHEA | dehydroepiandrosterone |
| DM | diabetes mellitus |
| DMPA | depot medroxyprogesterone acetate or Depo-Provera® |
| DUB | dysfunctional uterine bleeding |
| DVT | deep venous thrombosis |
| EPC | emergency postcoital contraception |
| FSH | follicle stimulating hormone |
| GA | gestational age |
| GIFT | gamete intrafallopian transfer |
| GnRH | gonadotropin-releasing hormone |
| GTD | gestational trophoblastic disease |
| GTN | gestational trophoblastic neoplasia |
| HERS | heart and estrogen/progestin replacement study |
| HMG | human menopausal gonadotropin |
| HPO | hypothalamic-pituitary-ovarian |
| HPV | human papillomavirus |
| HRT | hormone replacement therapy |
| HSG | hysterosalpingography |
| HSIL | high grade squamous intraepithelial lesion |
| HSV | herpes simplex virus |
| IBD | inflammatory bowel disease |
| ICSI | intracytoplasmic sperm injection |
| ITP | immune thrombocytopenic purpura |
| IUD | intrauterine device |
| IUI | intrauterine insemination |
| IUS | interauterine system |
| IVDU | intravenous drug use |
| IVF | *in vitro* fertilization |
| IVM | *in vitro* maturation |
| JRA | juvenile rheumatoid arthritis |
| LDH | lactate dehydrogenase |
| LEEP | loop electrosurgical excision procedure |
| LH | luteinizing hormone |
| LHRH | luteinizing hormone-releasing hormone |
| LMP | last menstrual period |
| LN | lymph node |
| LNMP | last normal menstrual period |
| LSIL | low grade squamous intraepithelial lesion |
| LVSI | lymphovascular space involvement |
| MRKH | Mayer-Rokitansky-Küster-Hauser |
| NK | natural killer |
| N/V | nausea/vomiting |
| OCP | oral contraceptive pill |
| OGTT | oral glucose tolerance test |
| PCOS | polycystic ovarian syndrome |
| PCR | polymerase chain reaction |
| PG | prostaglandin |
| PID | pelvic inflammatory disease |
| PMB | postmenopausal bleeding |
| PMDD | premenstrual dysphoric disorder |
| PMN | polymorphonuclear neutrophils |
| PMS | premenstrual syndrome |
| RPR | rapid plasma reagin |
| SCC | squamous cell carcinoma |
| SERMs | selective estrogen receptor modulator |
| SHBG | sex hormone binding globulin |
| SHG | sonohysterography |
| SPERM | selective progesterone receptor modulator |
| SSRIs | selective serotonin reuptake inhibitors |
| STI | sexually transmitted infections |
| TAH | total abdominal hysterectomy |
| TET | tubal embryo transfer |
| TH | total hysterectomy |
| TOT | tension-free transobturator tape |
| TSH | thyroid-stimulating hormone |
| TVT | tension-free vaginal tape |
| TZ | transformation zone |
| UAE | uterine artery embolization |
| U/S | ultrasound |
| UTI | urinary tract infection |
| VDRL | venereal disease research laboratory |
| VIN | vulvar intraepithelial neoplasia |
| VTE | venous thromboembolism |
| vWD | von Willebrand disease |
| W/D | withdrawal |
| WHI | Women's Health Initiative |
| ZIFT | zygote intrafallopian transfer |

# Basic Anatomy Review

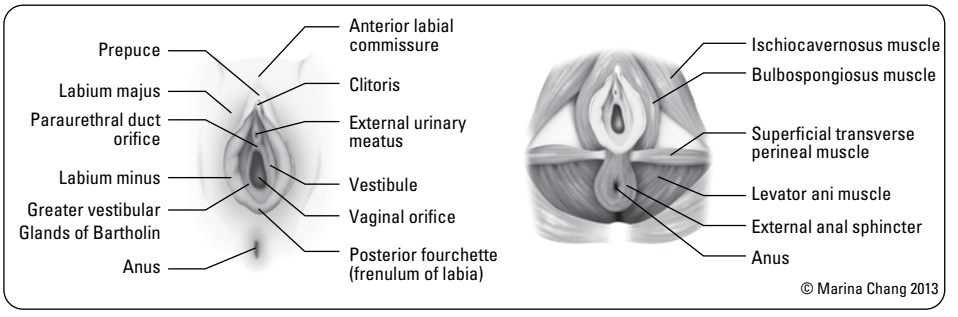



**Figure 1. Vulva and perineum**

## A. EXTERNAL GENITALIA

- blood supply: internal pudendal artery
- sensory innervation: pudendal nerve
- lymphatic drainage: inguinal nodes

## B. VAGINA

- muscular canal extending from cervix to vulva, anterior to rectum and posterior to bladder
- lined by rugated, stratified squamous epithelium
- upper vagina separated by cervix into anterior, posterior, and lateral fornices
- blood supply: vaginal branch of internal pudendal artery with anastamoses from uterine, inferior vesical, and middle rectal arteries

## C. UTERUS

- thick walled, muscular organ between bladder and rectum, consisting of two major parts:
  - uterine corpus
    - blood supply: uterine artery (branch of the internal iliac artery, anterior division)
  - cervix
    - blood supply: cervical branch of uterine artery
- supported by the pelvic diaphragm, the pelvic organs, and 4 paired sets of ligaments
  - round ligaments: travel from anterior surface of uterus, through broad ligaments, and inguinal canals then terminate in the labia majora
    - function: anteversion
    - blood supply: Sampson's artery (branch of uterine artery running through round ligament)
  - uterosacral ligaments: arise from sacral fascia and insert into posterior inferior uterus
    - function: mechanical support for uterus, prevent prolapse and contain autonomic nerve fibres
  - cardinal ligaments: extend from lateral pelvic walls and insert into lateral cervix and vagina
    - function: mechanical support, prevent prolapse
  - broad ligaments: pass from lateral pelvic wall to sides of uterus; contain fallopian tube, round ligament, ovarian ligament, nerves, vessels, and lymphatics

- infundibulopelvic ligament (suspensory ligament of the ovary): continuous tissue that connects ovary to pelvic wall
  - contains the ovarian artery, ovarian vein, ovarian plexus, and lymphatic vessels
- position of the uterus
  - anteverted (majority), retroverted, neutral

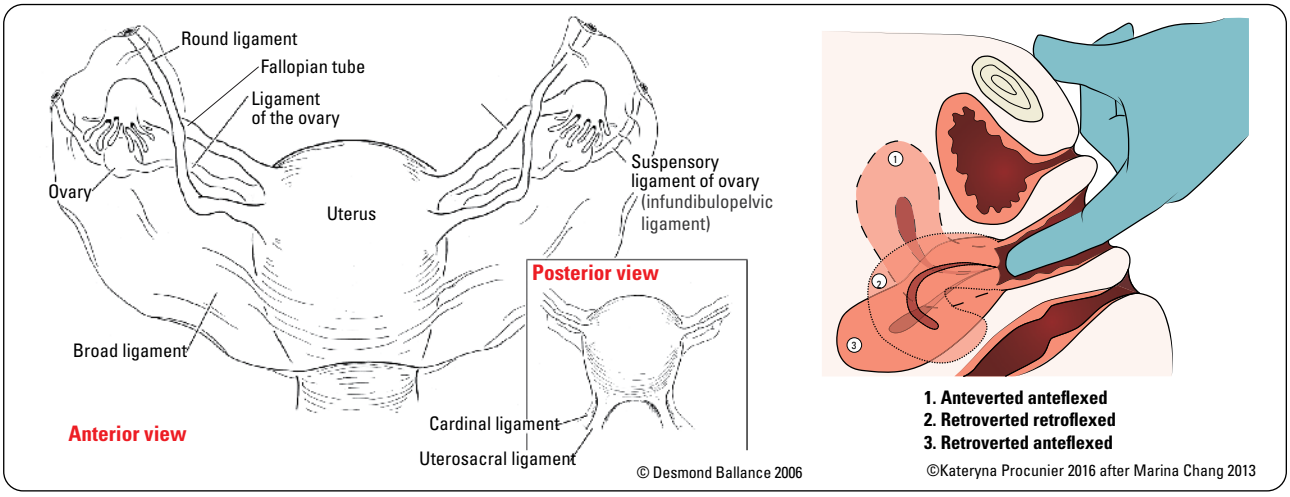



**Figure 2. Genital organs and positioning of the uterus**

## D. FALLOPIAN TUBES

- 8-14 cm muscular tubes extending laterally from the uterus to the ovary
- interstitial, isthmic, ampullary, and infundibular segments; terminates at fimbriae
- mesosalpinx: peritoneal fold that attaches fallopian tube to broad ligament
- blood supply: uterine and ovarian arteries

## E. OVARIES

- consist of cortex with ova and medulla with blood supply
- supported by infundibulopelvic ligament (suspensory ligament of ovary)
- mesovarium: peritoneal fold that attaches ovary to broad ligament
- blood supply: ovarian arteries (branches off of aorta), left ovarian vein (drains into left renal vein), right ovarian vein (drains into inferior vena cava)

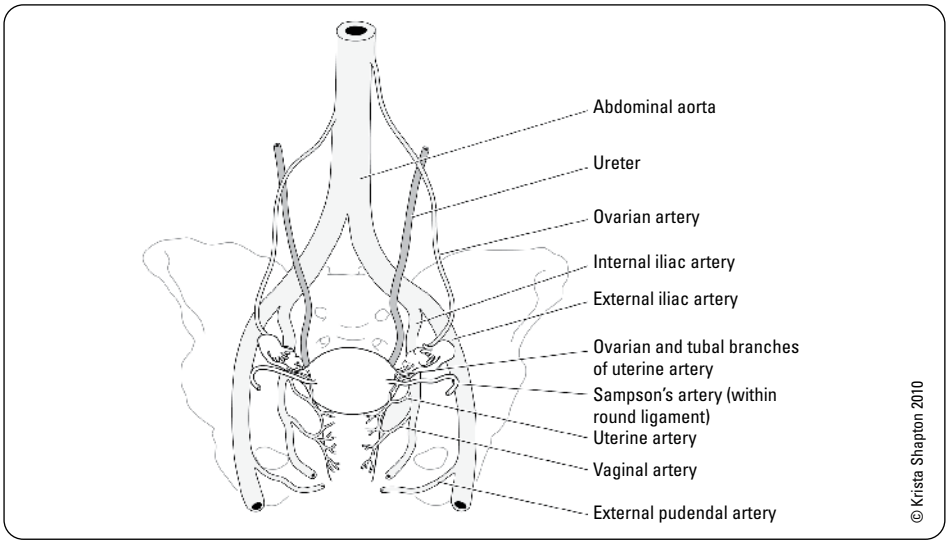



**Figure 3. Vascular supply**

**Determination of Uterine Position by Clinical Exam**

- If cervix faces anteriorly (under the urethra and less easily accessible), i.e. toward vaginal orifice, more likely RETROVERTED UTERUS
- If cervix faces posteriorly (easily accessible), i.e. toward sacrum or rectum, more likely ANTEVERTED UTERUS
- If uterus palpable on bimanual exam, more likely ANTEVERTED UTERUS

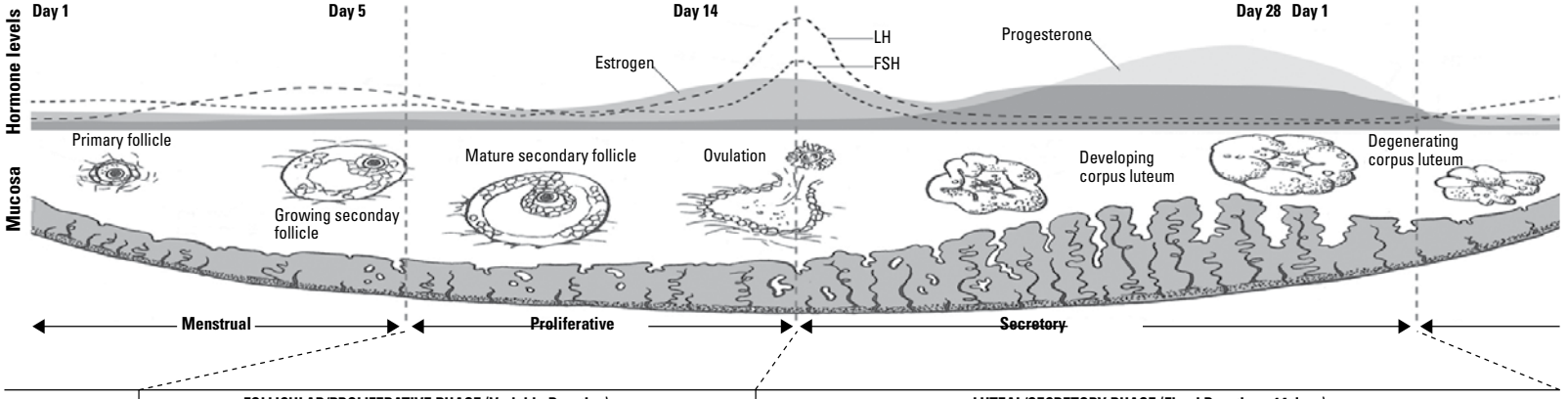
**"Water Under the Bridge"**
The ureters run posterior to the uterine arteries

**Common Anatomy Questions in the OR**

- **What is the origin of the left and right ovarian arteries?**
  Descending aorta
- **What are the drainage sites for the left and right ovarian veins?**
  Left to left renal vein, right to inferior vena cava
- **What is the most common place to locate the ureter?**
  Pelvic brim, medial leaf of the broad ligament as it passes under the uterine artery
- **Which artery runs under the round ligament?**
  Sampson's artery

# Menstruation

## Menstrual Cycle




| | FOLLICULAR/PROLIFERATIVE PHASE (Variable Duration) | | | LUTEAL/SECRETORY PHASE (Fixed Duration - 14 days) | | |
|---|---|---|---|---|---|---|
| | **Early** | **Mid** | **Late** | **OVULATION** | **Early-Mid** | **Late** |
| **Initiating Events** | ↓ E and ↓ P (from end of previous cycle) | ↑ FSH acts on ovarian granulosa cells | Growing follicles continue to secrete E | Sudden switch from negative to positive feedback (E and P now ↑ FSH & LH) | Switch back to negative feedback | No fertilized oocyte |
| **HPO Axis** | ↑ GnRH pulse frequency<br>↑ FSH<br>↑ LH pulse frequency | ↑ E from follicles (ovary) | | ↑↑ LH pulse amplitude (LH surge) | ↓ LH | |
| **Hormones** | | | ↑ E from follicles, especially from dominant follicle | E peaks → LH surge → ovulation | ↑ P from corpus luteum | ↓ P secondary to degeneration of corpus luteum |
| **Feedback on HPO Axis** | | Negative feedback E → ↓ FSH, ↓ LH | | Positive feedback: E and P → ↑ FSH, ↑ LH | Negative feedback P → ↓ FSH, ↓ LH | |
| **Ovaries** | ↑ FSH → follicular growth in 3-30 follicles | ↑ follicular growth (by reducing atresia) → ↑ E | Dominant follicle persists, remainder undergo atresia<br>Granulosa cells luteinize → produce P | ~36 h after LH surge, dominant follicle releases oocyte; corpus luteum (remnant of dominant follicle) produces P | | Cessation of P from corpus luteum |
| **Endometrium** | Menses from P withdrawal (from end of previous cycle) | | E builds up endometrium | | P stabilizes endometrium | Withdrawal of P → menses |
| **Cervical Mucus** | | Cervical mucus: Clear, ↑ amount, Spinnbarkeit 8-10 cm, more stringy | | | | Cervical mucus: Opaque, scant amount, Spinnbarkeit 1-2 cm |

© Tess Peters 2009 and Sonya Amim 2003

E = estrogen; FSH = follicle-stimulating hormone; GnRH = gondatropin-releasing hormone; HPO = hypothalamic pituitary-ovarian; LH = lutenizing hormone; P = progesterone

**Figure 4. Events of the normal menstrual cycle**

**CHARACTERISTICS**
- Menarche 10-15 yr
- Average 12.2 yr
- Entire cycle 28 ± 7 d with bleeding for 1-6 d
- 25-80 mL blood loss per cycle

**ESTROGEN**
ESTROGEN is the main hormone in the follicular/proliferative phase and is stimulated by FSH. As the level increases it acts negatively on FSH. The majority of estrogen is secreted by the dominant follicle

Estrogen effects
- On the follicles in the ovaries
  - Reduces atresia
- On the endometrium
  - Proliferation of glandular and stromal tissue
- On all target tissues
  - Decreases E receptors

**PROGESTERONE**
PROGESTERONE is the main hormone in the luteal/secretory phase and is stimulated by LH. Increased progesterone acts negatively on LH and is secreted by the corpus luteum (remnant of dominant follicle)

Progesterone effects
- On the endometrium
  - Cessation of mitoses (stops building endometrium up)
  - "Organization" of glands (initiates secretions from glands)
  - Inhibits macrophages, interleukin-8, and enzymes from degrading endometrium
- On all target tissues
  - Decrease E receptors (the "anti-estrogen" effect)
  - Decrease P receptors

# Stages of Puberty

- see Pediatrics, P31
- adrenarche: increased secretion of adrenal androgens; usually precedes gonadarche by 2 yr
- gonadarche: increased secretion of gonadal sex steroids; ~age 8 yr
- thelarche: breast development
- pubarche: pubic and axillary hair development
- menarche: onset of menses, usually following peak height velocity and/or 2 yr following breast budding

**Stages of Puberty**

**"Boobs, Pubes, Grow, Flow"**
Thelarche, Pubarche, Growth spurt, Menarche

**Tanner Stage**

**Thelarche**
1. None
2. Breast bud
3. Further enlargement of areolae and breasts with no separation of contours
4. 2º mound of areolae and papilla
5. Areolae recessed to general contour of breast – adult

**Pubarche**
1. None
2. Downy hair along labia only
3. Darker/coarse hair extends over pubis
4. Adult-type hair with no thigh involvement
5. Adult hair in distribution and type; extends over thighs. Not all patients achieve Tanner Stage 5. For image see Pediatrics, P32

# Premenstrual Syndrome

- synonyms: "ovarian cycle syndrome," "menstrual molimina" (moodiness)

## Etiology
- multifactorial: not completely understood; genetics likely play a role
- CNS-mediated neurotransmitter (serotonin, dopamine, GABA) interactions with sex steroids (P, E, and T)
- serotonergic dysregulation – currently most plausible theory

## Diagnostic Criteria for Premenstrual Syndrome
- at least one affective and one somatic symptom during the 5 d before menses in each of the three prior menstrual cycles
  - affective: depression, angry outbursts, irritability, anxiety, confusion, social withdrawal
  - somatic: breast tenderness or swelling, abdominal bloating, headache, swelling of extremities, joint or muscle pain, or weight gain
- symptoms relieved within 4 d of onset of menses and do not recur until at least day 13 of cycle
- symptoms present in the absence of any pharmacologic therapy, hormone ingestion, drug or alcohol use
- symptoms occur reproducibly during 2 cycles of prospective recording
- patient suffers from identifiable dysfunction in social or occupational performance

**Premenstrual Syndrome**
Physiological and emotional disturbances that occur 1-2 wk prior to menses and last until a few days after onset of menses; common symptoms include depression, irritability, tearfulness, and mood swings

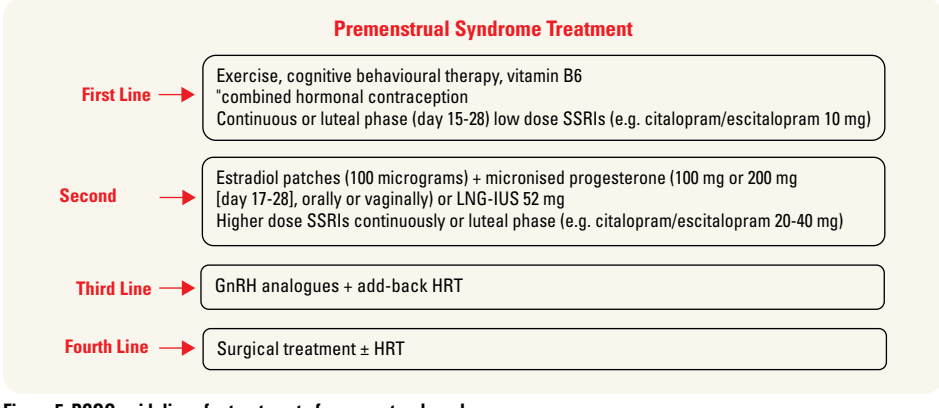



**Figure 5. RCOG guidelines for treatment of premenstrual syndrome**
Adapted from source: https://www.rcog.org.uk/globalassets/documents/guidelines/gt48managementpremensturalsyndrome.pdf

# Premenstrual Dysphoric Disorder

## Clinical Feature
- irritability, depressed mood
- breast pain and bloating

## Diagnostic Criteria for Premenstrual Dysphoric Disorder
- at least 5 of the following 11 symptoms during most menstrual cycles of the last year (with at least 1 of the first 4)
  - depressed mood or hopelessness
  - anxiety or tension
  - affective instability
  - anger or irritability
  - decreased interest in activities
  - difficulty concentrating
  - lethargy
  - change in appetite
  - hypersomnia or insomnia
  - feeling overwhelmed
  - physical symptoms: breast tenderness/swelling, headaches, joint/muscle pain, bloating, or weight gain
- symptoms cause significant distress and/or interfere with social or occupational functioning
- symptoms must be present during the week prior to menses and resolve within a few days after onset of menses
- may be superimposed on other psychiatric disorders, provided it is not merely an exacerbation of another disorder

# Common Investigations and Procedures

## Imaging

### Ultrasound (U/S)

- transabdominal or transvaginal U/S is the imaging modality of choice for pelvic structures
- transvaginal U/S provides better resolution of uterus and adnexal structures
  - detects early pregnancy if β-hCG ≥1500 (β-hCG must be ≥6500 for transabdominal U/S)
- may be used to identify pelvic pathology
  - identify ectopic pregnancy, intrauterine pregnancy
  - assess uterine, adnexal, cul-de-sac, and ovarian masses (e.g. solid or cystic)
  - determine endometrial thickness, locate/characterize fibroids
  - monitor follicles during assisted reproduction
  - assess endometrial lining in postmenopausal women

Every woman of childbearing age presenting to ER with abdominal or pelvic pain should have β-hCG measured

## Endometrial Biopsy

- performed in the office using an endometrial suction curette (pipelle) guided through the cervix to aspirate fragments of endometrium
  - pre-treatment with misoprostol (Cytotec®) is optional
- more invasive procedure (i.e. D&C) may be done in the office or operating room ± hysteroscopy. This may be required if endometrial biopsy is not possible in the office setting or if there is suspicion for an endometrial polyp
- indications
  - AUB/PMB
    - age >40
    - risk factors for or history of endometrial cancer
    - failure of medical treatment
    - significant intermenstrual bleeding
    - consider in women with infrequent menses suggesting anovulatory cycles

## Hysterectomy

### Indications

- uterine fibroids
- endometriosis, adenomyosis
- uterine prolapse
- pelvic pain
- AUB
- cancer (endometrium, ovaries, fallopian tubes, cervix)

### Complications

- general anesthetic
- bleeding
- infection
- injury to other organs (ureter, bladder, rectum)
- loss of ovarian function (if ovaries removed, iatrogenic menopause)

### Approaches

1. Open (abdominal approach): uterus removed via transverse (Pfannenstiel) or midline laparotomy
2. Minimally invasive approaches
   - vaginal hysterectomy: entire procedure performed through the vagina. No abdominal incisions
   - laparoscopic-assisted vaginal hysterectomy: vascular pedicles are divided by a combination of laparoscopic and vaginal approaches
   - total laparoscopic hysterectomy: all vascular pedicles including the colpotomy approached laparoscopically and removed through the vagina
   - robotic: a type of laparoscopic approach. May be advantageous in high BMI patients. More costly

**No. 377 – Hysterectomy for Benign Gynaecological Indications**
J Obstet Gynaecol Can 2019;41(4):543-557
**Summary:**

1. Hysterectomy should be approached by either vaginal, laparoscopic, or open routes
2. Correction of preoperative anemia (hemoglobin <120 g/L), preoperative antibiotic prophylaxis, and measures to decrease risk of venous thromboembolism are recommended
3. In patients with endometriosis, full excision of local endometriosis should be performed concurrently
4. Opportunistic salpingectomy can be considered at the time of hysterectomy, but the planned surgical approach should not be changed for this sole purpose
5. Urinary tract injury is a known complication of hysterectomy and there should be a low threshold for further investigation in cases where injury is suspected- consider routine cystoscopy

Women should be counselled about the benefits and risks of removing the ovaries, the risk of ovarian cancer versus the long-term health implications of earlier menopause

**Table 1. Classification of Hysterectomy**

| Classification | Tissues Removed | Indications |
|---|---|---|
| **Subtotal Hysterectomy** | Uterus | Inaccessible cervix (e.g. adhesions)<br>Patient choice/preference<br>Severe endometriosis |
| **Total Hysterectomy (extrafascial simple hysterectomy/type 1)** | Uterus, cervix, uterine artery ligated at uterus | Uterine fibroids<br>Endometriosis<br>Adenomyosis<br>Heavy menstrual bleeding<br>DUB |
| **Total Hysterectomy (extrafasical simple hysterectomy/type 1) + Bilateral Salpingo-Oophorectomy** | Uterus, cervix, uterine artery ligated at uterus, fallopian tubes, ovaries | Endometrial cancer<br>Malignant adnexal masses<br>Consider for endometriosis |
| **Modified Radical Hysterectomy (type 2)** | Uterus, cervix, proximal 1/3 parametria, uterine artery ligated medial to the ureter, mid point of uterosacral ligaments, and upper 1-2 cm vagina | Cervical cancer (up to stage 1B1) |
| **Radical Hysterectomy (type 3)** | Uterus, cervix, entire parametria, uterine artery ligated at its origin from internal iliac artery, uterosacral ligament at most distal attachment (rectum), and upper 1/3-1/2 vagina | Cervical cancer |

# Disorders of Menstruation

## Amenorrhea

### Differential Diagnosis of Amenorrhea

**Table 2. Differential Diagnosis of Primary Amenorrhea**

| With Secondary Sexual Development | | Without Secondary Sexual Development | |
|---|---|---|---|
| **Normal breast and pelvic development** | **Normal breast, abnormal uterine development** | **High FSH (hypergonadotropic hypogonadism)** | **Low FSH (hypogonadotropic hypogonadism)** |
| Hypothyroidism<br>Hyperprolactinemia<br>PCOS<br>Hypothalamic dysfunction | Androgen insensitivity<br>Anatomic abnormalities<br>Müllerian agenesis, uterovaginal septum, imperforate hymen | Gonadal dysgenesis<br>Abnormal sex chromosome (Turner's XO)<br>Normal sex chromosome (46XX, 46XY) | Constitutional delay (rare in girls)<br>Congenital abnormalities<br>Isolated GnRH deficiency<br>Pituitary failure (Kallman syndrome, head injury, pituitary adenoma, etc.)<br>Acquired endocrine disorders (type 1 DM)<br>Pituitary tumours<br>Systemic disorders (IBD, JRA, chronic infections, etc.)<br>Functional hypothalamic amenorrhea |

**Most Common Causes of Primary Amenorrhea**
1. Müllerian agenesis
2. Abnormal sex chromosomes (Turner's syndrome)
3. Functional hypothalamic amenorrhea

**Table 3. Differential Diagnosis of Secondary Amenorrhea**

| With Hyperandrogenism | Without Hyperandrogenism |
|---|---|
| PCOS<br>Autonomous hyperandrogenism (androgen secretion independent of the HPO axis)<br>Ovarian: tumour, hyperthecosis<br>Adrenal androgen-secreting tumour<br>Late onset or mild congenital adrenal hyperplasia (rare) | Hypergonadotropic hypogonadism (i.e. primary ovarian insufficiency: high FSH, low estradiol)<br>Idiopathic<br>Autoimmune: type 1 DM, autoimmune thyroid disease, Addison's disease<br>Iatrogenic: cyclophosphamide drugs, radiation<br>Hyperprolactinemia<br>Endocrinopathies: most commonly hyper or hypothyroidism<br>Hypogonadotropic hypogonadism (low FSH):<br>Pituitary compression or destruction: pituitary adenoma, craniopharyngioma, lymphocytic hypophysitis, infiltration (sarcoidosis), head injury, Sheehan's syndrome<br>Functional hypothalamic amenorrhea (often related to stress excessive exercise and/or anorexia) |

Functional hypothalamic amenorrhea is the most common cause of secondary amenorrhea

## Investigations

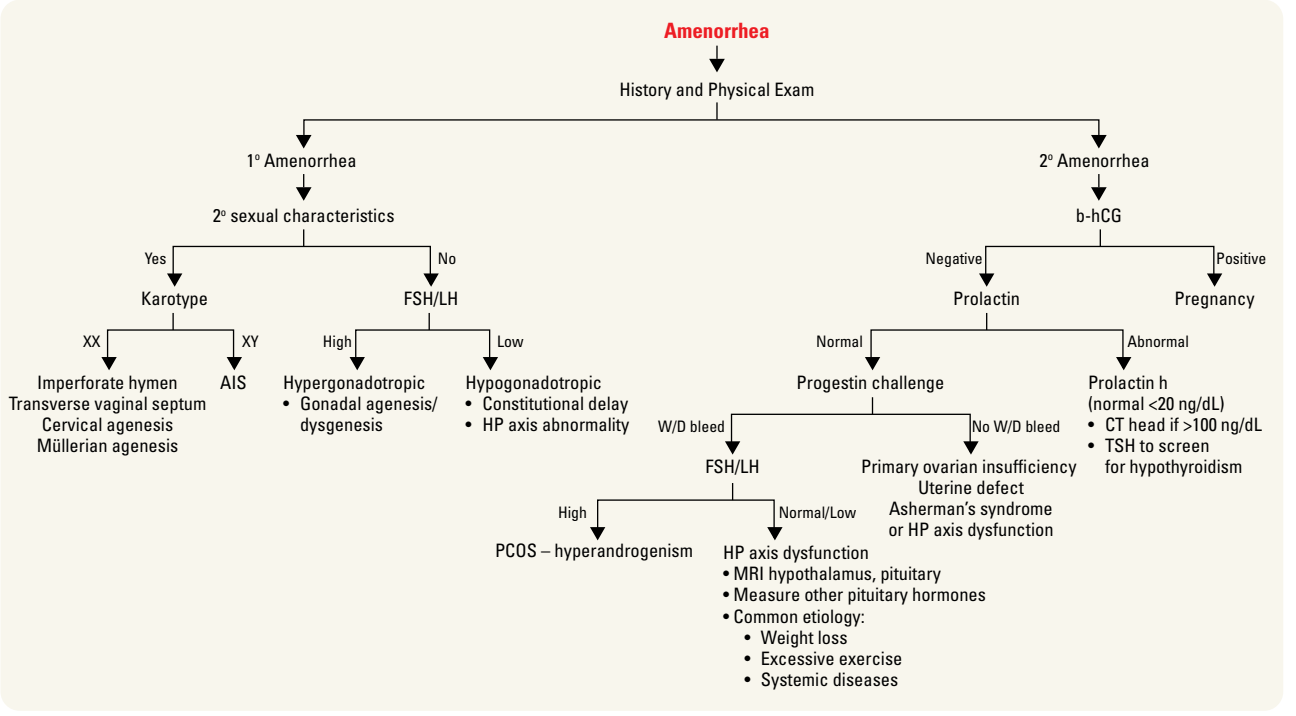



**Figure 6. Diagnostic approach to amenorrhea**

- β-hCG, hormonal workup (TSH, prolactin, FSH, LH, androgens, estradiol)
- progesterone challenge to assess estrogen status
  - medroxyprogesterone acetate (Provera®) 10 mg PO OD for 10-14 d
  - any uterine bleed within 2-7 d after completion of Provera® is considered to be a positive test/ withdrawal bleed
    - withdrawal bleed suggests presence of adequate estrogen to thicken the endometrium; thus withdrawal of progesterone results in bleeding
    - if no bleeding occurs, this may be secondary to inadequate estrogen (hypoestrogenism), excessive androgens, or progesterones (decidualization) or pregnancy
- karyotype: indicated if primary ovarian insufficiency or absent puberty
- U/S to confirm normal anatomy, identify PCOS

**Prolactinoma Symptoms**
Galactorrhea, visual changes, headache

## Treatment

**Table 4. Management of Amenorrhea**

| Etiology | Management |
|---|---|
| **1° AMENORRHEA** | |
| Androgen insensitivity syndrome | Gonadal resection after puberty |
| | Psychological counselling |
| | Creation of neo-vagina with dilation |
| Anatomical | |
| Imperforate hymen | Surgical management |
| Transverse vaginal septum | Surgical management |
| Cervical agenesis | Suppression and ultimately hysterectomy |
| Müllerian dysgenesis (MRKH syndrome) | Psychological counselling |
| | Creation of neo-vagina with dilation |
| | Diagnostic study to confirm normal urinary system and spine |

**Primary Amenorrhea**
No menses by age 13 in absence of 2° sexual characteristics, or no menses by age 15 with 2° sexual characteristics, or no menses 2 yr after thelarche

**Secondary Amenorrhea**
No menses for >6 mo or 3 cycles after documented menarche

**Table 4. Management of Amenorrhea** (continued)

| Etiology | Management |
|---|---|
| **2° AMENORRHEA** | |
| HP-axis dysfunction | **Identify modifiable underlying cause**<br>Combined OCP to decrease risk of osteoporosis, maintain normal vaginal and breast development (NOT proven to work) |
| Hyperprolactinemia | MRI/CT head to rule out lesion<br>If no demonstrable lesions by MRI<br>Bromocriptine, cabergoline if fertility desired<br>Combined OCPs if no fertility desired<br>Demonstrable lesions by MRI: surgical management |
| Polycystic ovarian syndrome | See *Polycystic Ovarian Syndrome*, GY23 |
| Premature ovarian failure | Screen for DM, hypothyroidism, hypoparathyroidism, hypocorticolism<br>Hormonal therapy with estrogen + progestin to decrease risk of osteoporosis; can use OCP after induction of puberty |
| Uterine defect | Evaluation with hysterosalpingography or sonohysterography |
| Asherman's syndrome | Hysteroscopy: excision of synechiae |

2° amenorrhea is pregnancy until proven otherwise

# Abnormal Uterine Bleeding

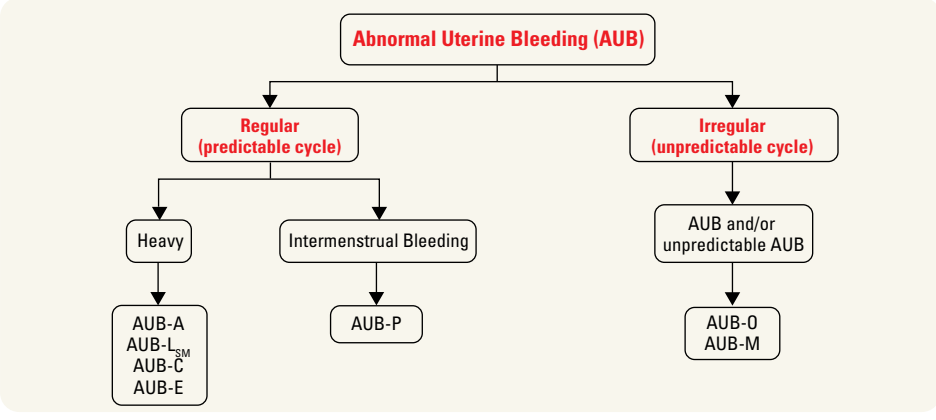



**Figure 7. Diagnostic approach to abnormal uterine bleeding**

## Approach

- menstrual bleeding should be evaluated by ascertaining: frequency/regularity of menses, duration, volume of flow, impact on quality of life, and timing (inter or premenstrual or breakthrough)
- is it regular?
  - regular: cycle to cycle variability of <20 d – "Can you predict your menses within 20 days?"
  - irregular: cycle to cycle variability of ≥20 d
- is it heavy?
  - ≥80 cc of blood loss per cycle or
  - ≥8 d of bleeding per cycle or
  - bleeding that significantly affects quality of life
- is it structural?
  - PALM
- is it non-structural?
  - COEIN

Postmenopausal bleeding is endometrial cancer until proven otherwise

**Abnormal Uterine Bleeding**
Change in frequency, duration, or amount of menstrual flow that affects quality of life

**Table 5. AUB – Etiologies, Investigations, and Management**

| Etiology | Investigations | Management |
|---|---|---|
| | **STRUCTURAL** | |
| **Polyps (AUB-P)** | Transvaginal sonography<br>Saline infusion sonohysterography | Polypectomy (triage based on symptoms,polyp size, histopathology and patient age) |
| **Adenomyosis (AUB-A)** | Transvaginal sonography<br>MRI | See *Adenomyosis*, GY13 |
| **Leiomyoma (AUB-L)**<br>**Submucosal (AUB-Lsm)**<br>**Other (AUB-Lo)** | Transvaginal sonography<br>Saline infusion sonohysterography<br>Diagnostic hysteroscopy | See *Fibroids (Leiomyomata)*, GY13 |
| **Malignancy and Hyperplasia (AUB-M)** | Transvaginal sonography<br>Endometrial biopsy for all women >40 yr with AUB, for women <40 yr with persistent AUB or endometrial cancer risk factors | Dependent on diagnosis |
| | **NON-STRUCTURAL** | |
| **Coagulopathy (AUB-C)** | CBC, coagulation profile (especially in adolescents), vWF, Ristocetin cofactor, factor VIII | Dependent on diagnosis (hormonal modulation (e.g. OCP), Mirena IUS, endometrial ablation) |
| **Ovulatory dysfunction (AUB-O)** | Bloodwork: β-hCG, ferritin, prolactin, FSH, LH, serum androgens (free testosterone, DHEA), progesterone, 17-hydroxy progesterone, TSH, free T4<br>pelvic ultrasound | See *Infertility*, GY22 |
| **Endometrial (AUB-E)** | Endometrial biopsy | Tranexamic acid<br>Hormonal modulation (e.g. OCP)<br>Mirena IUS<br>Endometrial ablation |
| **Iatrogenic (AUB-I)** | Transvaginal sonography (rule out forgotten IUD)<br>Review OCP/HRT use<br>Review meds (especially neuroleptic use) | Remove offending agent |
| **Not yet classified (AUB-N)** | — | — |

## Treatment

- resuscitate patient if hemodynamically unstable
- treat underlying disorders
  - if anatomic lesions and systemic disease have been ruled out, consider AUB
- medical
  - mild AUB
    - NSAIDs
    - anti-fibrinolytic (e.g. Cyklokapron®) at time of menses
    - combined hormonal contraceptive
    - progestins (Provera®) on first 10-14 d of each month or every 3 mo if AUB-O
    - Mirena® IUD
    - correct anemia - iron
  - acute, severe AUB
    - replace fluid losses, consider admission

    a) estrogen (Premarin®) 25 mg IV q4h x 24 h with Gravol® 50 mg IV/PO q4h or anti-fibrinolytic (e.g. Cyklokapron®) 10 mg/kg IV q8h (rarely used)

    b) tapering OCP regimen, 35 μg pill tid x7d then taper to 1 pill/d for 3wk with Gravol® 50 mg IV/PO q4h
      - or taper to 1 tab tid x 2 d → bid x 2 d → OD (more commonly used)
    - after (a) or (b), maintain patient on monophasic OCP for next several months or consider alternative medical treatment
      - medical (can also consider):
        - high dose progestins
        - danazol (Danocrine®)
        - GnRH agonsits (e.g. Lupron ®) with add-back if taken for >6 mo
        - ulipristal acetate
- surgical
  - endometrial ablation
    - if finished childbearing
    - repeat procedure may be required if symptom recur, especially if <40 yr
  - hysterectomy: definitive treatment

# Dysmenorrhea

## Etiology
- primary/idiopathic
- secondary (acquired)
  - endometriosis
  - adenomyosis
  - uterine polyps
  - uterine anomalies (e.g. non-communicating uterine horn)
  - leiomyoma
  - intrauterine synechiae
  - ovarian cysts
  - cervical stenosis
  - imperforate hymen, transverse vaginal septum
  - pelvic inflammatory disease
  - IUD (copper)
  - foreign body

**Primary Dysmenorrhea**
Recurrent crampy lower abdominal pain during menses in the absence of demonstrable disease

**Secondary Dysmenorrhea**
Pain during menses that can be attributed to an underlying disorder (endometriosis, adenomyosis, fibroids)

**Table 6. Comparison of Primary and Secondary Dysmenorrhea**

| | Primary Dysmenorrhea | Secondary Dysmenorrhea |
|---|---|---|
| **Features** | Recurrent, crampy lower abdominal pain that occurs during menses in the absence of demonstrable disease | Similar features as primary dysmenorrhea but with an underlying disorder that can account for the symptoms, such as endometriosis, adenomyosis or uterine fibroids |
| **Signs and Symptoms** | Colicky pain in abdomen, radiating to the lower back, labia, and inner thighs beginning hours before onset of bleeding and persisting for hours or days (48-72 h)<br>Associated symptoms: N/V, altered bowel habits, headaches, fatigue (prostaglandin-associated) | Associated dyspareunia, abnormal bleeding, infertility |
| **Diagnosis** | Assess for associated dyspareunia, abnormal bleeding, infertility (signs of 2° dysmenorrhea)<br>Rule out underlying pelvic pathology and confirm cyclic nature of pain<br>Pelvic examination not required; indicated for patients not responding to therapy or with signs of organic pathology | Bimanual exam: uterine or adnexal tenderness, fixed uterine retroflexion, uterosacral nodularity, pelvic mass, or enlarged irregular uterus (findings are rare in women <20 yr)<br>U/S, laparoscopy and hysteroscopy may be necessary to establish the diagnosis<br>Vaginal and cervical cultures may be required |
| **Treatment** | Regular exercise, local heat<br>NSAIDs: should be started before onset of pain<br>Combined hormonal contraceptives with continuous or extended use: suppress ovulation/ reduce menstrual flow | Treat underlying cause |

# Endometriosis

## Definition
- the presence of endometrial tissue (glands and stroma) outside of the uterine cavity
- chronic condition, resolving only with menopause

## Etiology
- not fully understood; proposed mechanisms include (combination likely involved):
  - retrograde menstruation (Sampson's theory)
  - immunologic: decreased NK cell activity limiting clearance of transplanted endometrial cells from pelvic cavity (may be due to decreased NK cell activity)
  - metaplasia of coelomic epithelium
  - extrapelvic disease may be due to aberrant vascular or lymphatic dissemination of cells
    - e.g. ovarian endometriosis may be due to direct lymphatic flow from uterus to ovaries

**Differential Diagnoses**
- Chronic PID, recurrent acute salpingitis
- Hemorrhagic corpus luteum
- Benign/malignant ovarian neoplasm
- Ectopic pregnancy

**Classic Triad of Endometriosis**
- Dysmenorrhea
- Dyspareunia (cul-de-sac, uterosacral ligament)
- Dyschezia (uterosacral ligament, cul-de-sac, rectosigmoid attachment)

## Epidemiology
- incidence: 15-30% of pre-menopausal women
- mean age at presentation: 25-30 yr
- regresses after menopause

## Risk Factors
- family history (7-10x increased risk if affected 1st degree relative)
- obstructive anomalies of the genital tract (earlier onset) – resolves with treatment of anomaly
- nulliparity
- age >25 yr

## Sites of Occurrence

- ovaries: 60% patients have ovarian involvement
- broad ligament, vesicoperitoneal fold
- peritoneal surface of the cul-de-sac, uterosacral ligaments
- rectosigmoid colon, appendix
- rarely may occur in sites outside abdomen/pelvis, including lungs

## Clinical Features

- may be asymptomatic and can occur with one of 3 presentations

**1. pain**

- menstrual symptoms
  - cyclic symptoms due to growth and bleeding of ectopic endometrium, usually precede menses (24-48 h) and continue throughout and after flow
  - secondary dysmenorrhea
  - sacral backache with menses
  - pain may eventually become chronic, worsening perimenstrually
  - deep dyspareunia
- bowel and bladder symptoms
  - frequency, dysuria, hematuria
  - cyclic diarrhea/constipation, hematochezia, dyschezia (suggestive of deeply infiltrating disease)

**2. infertility**

- 30-40% of patients with endometriosis will be infertile
- 15-30% of those who are infertile will have endometriosis

**3. mass (endometrioma)**

- ovarian mass can present with any of above symptoms or be asymptomatic
- physical examination:
  - tender nodularity of uterine ligaments and cul-de-sac felt on rectovaginal exam
  - fixed retroversion of uterus
  - firm, fixed adnexal mass (endometrioma: an endometriotic cyst encompassing ovary)

## Investigations

- definitive diagnosis can be made based on:
  - direct visualization of lesions typical of endometriosis at laparoscopy
  - biopsy and histologic exam of specimens (2 or more of: endometrial epithelium, glands, stroma, hemosiderin-laden macrophages)
- laparoscopy
  - mulberry spots: dark blue or brownish-black implants on the uterosacral ligaments, cul-de-sac, or anywhere in the pelvis
  - endometrioma: "chocolate" cysts on the ovaries
  - "powder-burn" lesions on the peritoneal surface
  - early white lesions and clear blebs
  - peritoneal "pockets"
- CA-125 (cancer antigen 125)
  - may be elevated in patients with endometriosis but should NOT be used as a diagnostic test

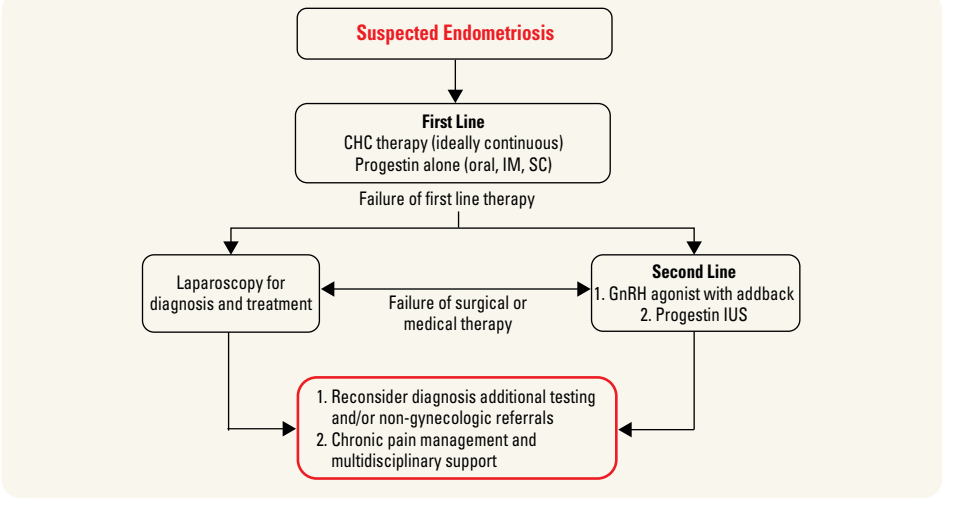



**Figure 8. SOGC guidelines for treatment of endometriosis**

**Endometriosis – Take Home Points**

- Suggestive history even with a negative exam should be considered adequate for a presumptive diagnosis
- Pelvic pain that is not primary dysmenorrhea should be considered endometriosis until proven otherwise
- Medical management is the mainstay of endometriosis

## Treatment

- surgical confirmation of disease is NOT required prior to starting medical management. Asymptomatic endometriosis does not require treatment. Management depends on certainty of the diagnosis, severity of symptoms, extent of disease, desire for future fertility, and impact to GI/GU systems (e.g. intestinal obstruction)

- medical
  - NSAIDs (e.g. naproxen sodium – Anaprox®)
  - 1st line
    - cyclic/continuous estrogen-progestin (OCP)
    - progestin (IM medroxyprogesterone (Depo-Provera®) or oral dienogest (Visanne®))
    - Mirena® IUS
  - 2nd line
    - GnRH-agonist (e.g. leuprolide (Lupron®)): suppresses pituitary
      - side effects: hot flashes, vaginal dryness, reduced libido
      - use >6 mo: include add-back progestin or estrogen to prevent decreased BMD, reduce vasomotor side-effects
    - danazol (Danocrine®): weak androgen
      - side effects: weight gain, fluid retention, acne, hirsutism, voice change
- surgical
  - conservative laparoscopy using laser, electrocautery ± laparotomy
    - ablation/resection of implants, lysis of adhesions, ovarian cystectomy of endometriomas
  - definitive: bilateral salpingo-oophorectomy ± hysterectomy
  - best time to become pregnant is immediately after conservative surgery
  - if patient is not planning to become pregnant post-op, suppress ovulation medically to prevent recurrence

# Adenomyosis



- synonym: "endometriosis interna" (uterine wall may be diffusely involved)



**Adenomyosis**
Extension of areas of endometrial glands and stroma into the myometrium

### Epidemiology
- 15% of females >35 yr old; found in 20-40% of hysterectomy specimens
- mean age at presentation: 40-50 yr old (older age group than seen in endometriosis)
- adenomyosis is a common histologic finding in asymptomatic patients

### Clinical Features
- often asymptomatic
- heavy menstrual bleeding, secondary dysmenorrhea, pelvic discomfort
- dyspareunia, dyschezia
- uterus symmetrically bulky, usually <14 cm
- Halban sign: tender, softened uterus on premenstrual bimanual exam



Final diagnosis of adenomyosis is based on pathologic findings, but predictably identified on MRI

### Investigations
- clinical diagnosis
- U/S or MRI can be helpful
- endometrial sampling to rule out other pathology

### Treatment
- medical
  - iron supplements for anemia
  - analgesics, NSAIDs
  - Mirena® IUS
  - CHC, medroxyprogesterone (Depo-Provera®) – limited evidence for efficacy
  - GnRH agonists (e.g. leuprolide (Lupron ®))
  - low dose danazol 100-200 mg PO OD (trial x 4 mo)
- surgical
  - definitive: hysterectomy – treatment of choice in women who have completed childbearing

# Fibroids





**Leiomyomata/Fibroids**
Benign smooth muscle tumour of the uterus (most common gynecological tumour)

### Epidemiology
- diagnosed in approximately 40-50% of pre-menopausal women >35 yr
- more common in African Americans, where they are also larger and occur at earlier age
- common indication for major surgery in females
- minimal malignant potential (1:1000)
- typically regress after menopause



Submucosal leiomyomata are most symptomatic (bleeding, infertility)

### Pathogenesis
- estrogen stimulates monoclonal smooth muscle proliferation
- progesterone stimulates production of proteins that inhibit apoptosis
- degenerative changes (occur when tumour outgrows blood supply)
  - fibroids can degenerate, become calcified, develop sarcomatous component, or obtain parasitic blood supply



The effect of pregnancy on fibroid size is variable

## Clinical Features

- majority asymptomatic (60%), often discovered as incidental finding on pelvic exam or U/S
- abnormal uterine bleeding (30%): dysmenorrhea, heavy menstrual bleeding
- pressure/bulk symptoms (20-50%)
  - pelvic pressure/heaviness
  - increased abdominal girth
  - urinary frequency and urgency
  - constipation, bloating (rare)
  - acute urinary retention (extremely rare, but surgical emergency!)
- acute pelvic pain
  - fibroid degeneration
  - fibroid torsion (if pedunculated subserosal)
- infertility, recurrent pregnancy loss
- pregnancy complications (potential enlargement and increased pain, obstructed labour, difficult C-section)

## Investigations

- bimanual exam: uterus asymmetrically enlarged, usually mobile
- CBC: anemia
- U/S: to confirm diagnosis and assess location of fibroids
- sonohysterogram: useful for differentiating endometrial polyps from submucosal fibroids, or for assessing intracavitary growth
- endometrial biopsy to rule out uterine cancer for abnormal uterine bleeding (especially if age >40 yr)
- occasionally MRI is used for pre-operative planning (e.g. before myomectomy)

## Treatment

- only if symptomatic (heavy menstrual bleeding, menometrorrhagia, bulk symptoms), rapidly enlarging or intracavitary
- treat anemia if present
- conservative approach (watch and wait) if:
  - symptoms absent or minimal
  - fibroids <6-8 cm or stable in size
  - not submucosal (submucosal fibroids are more likely to be symptomatic)
  - currently pregnant due to increased risk of bleeding (follow-up U/S if symptoms progress)
- medical approach to treat AUB-L
  - antiprostaglandins (ibuprofen, other NSAIDs)
  - tranexamic acid (Cyklokapron®)
  - CHC, IUS or Depo-Provera®
  - GnRH agonist: leuprolide (Lupron®)
    - often used for 3 mo preoperatively to increase Hb and reduce fibroid size
    - reduces bleeding, shrinks fibroids, and corrects anemia
    - can be used long-term to bridge to menopause in combination with add-back progestin or estrogen
  - ulipristal acetate (Fibristal ®): a selective progesterone receptor agonist
    - 5 mg daily for 3 mo
    - reduces bleeding, shrinks fibroids
    - repeat courses only if patient not eligible for surgery; patients must menstruate between courses
    - associated with benign, non-physiological endometrial changes (selective progesterone receptor modulator-associated endometrial changes (PAEC)) which are reversible with discontinuation of therapy
    - note: rare side effect of liver failure. Screen for liver disease prior to prescribing, and monitor liver function before, during, and after treatment courses. Do not prescribe in patients with underlying liver disorder
- interventional radiology approach
  - uterine artery embolization (UAE) occludes both uterine arteries, shrinks fibroids by 50% at 6 mo; improves heavy bleeding in 90% of patients within 1-2 mo; not an option in women considering childbearing
    - higher risk of surgical re-intervention than with surgical approaches
- surgical approach
  - myomectomy (hysteroscopic, transabdominal, or laparoscopic)
  - hysteroscopic resection of fibroid and endometrial ablation for AUB-Lsm
  - hysterectomy (see *Hysterectomy*, GY6)
  - note: avoid operating on fibroids during pregnancy (due to vascularity and potential pregnancy loss); expectant management usually best

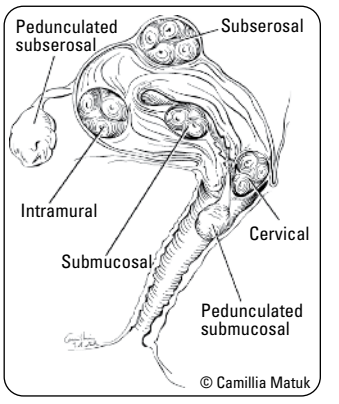



**Figure 9. Possible anatomic locations of uterine leiomyomata**

**Ulipristal Acetate vs. Leuprolide Acetate for Uterine Fibroids**
NEJM 2012;366:421-432
**Study**: Phase III, double-blind RCT of the efficacy and side-effect profile of ulipristal acetate versus those of leuprolide acetate for the treatment of symptomatic uterine fibroids before surgery.
**Outcomes**: Control of uterine bleeding at week 13 was the primary outcome. Secondary outcomes included bleeding pattern, amenorrhea, changes in fibroid/uterine volume, and global pain score.
**Patients**: 307 premenopausal women with symptomatic fibroids and excessive uterine bleeding were randomly assigned to oral ulipristal acetate (5 mg or 10 mg) or intramuscular injections of leuprolide acetate.
**Results**: Control of bleeding at week 13 was not significantly different between the treatment groups. All three treatments reduced uterine volume, although this decrease was significantly greater in the leuprolide group (47% reduction) than in the ulipristal groups (20-22%). 40% of the leuprolide group reported moderate-to-severe hot flashes, but only 11% (5 mg) and 10% (10 mg) of the ulipristal groups did.
**Conclusions**: Oral ulipristal acetate (5 mg or 10 mg) is noninferior to intramuscular leuprolide acetate for control of uterine bleeding due to fibroids and has a better side-effect profile.

**Uterine artery embolization for symptomatic uterine fibroids**
Cochrane Database Syst Rev. 2014, 12: CD005073
**Purpose**: To compare outcomes of uterine artery embolization (UAE) to other medical or surgical therapies for symptomatic uterine fibroids. Primary outcomes were patient satisfaction and live birth rate.
**Results**: Seven RCTs with 793 women were included. There was no evidence of a difference in the primary outcomes or risk of major complications between the interventions. UAE was associated with a higher risk of minor complications and the need for additional surgical intervention within two years.
**Conclusions**: No significant differences in patient satisfaction or major complications in UAE compared to surgical intervention. UAE is associated with an increased risk of surgical re-intervention.

# Contraception

• see Family Medicine, FM20

**Table 7. Classification of Contraceptive Methods**

| Type | Effectiveness (Perfect Use, Typical Use*) |
|---|---|
| **Physiological** | |
| Withdrawal/coitus interruptus | 96%, 77% |
| Rhythm method/calendar/mucus/symptothermal | 76% |
| Lactational amenorrhea | 98% (first 6 mo postpartum) |
| Chance – no method used | 15% |
| Abstinence of all sexual activity | 100% |
| **Barrier Methods** | |
| Condom alone | 98%, 82% |
| Spermicide alone | 82%, 72% |
| Sponge – Parous | 80%, 76% |
| – Nulliparous | 91%, 88% |
| Diaphragm with spermicide | 94%, 88% |
| Female condom | 95%, 79% |
| Cervical cap – Parous | 74%, 68% |
| – Nulliparous | 91%, 84% |
| **Hormonal** | |
| OCP | 99.7%, 92% |
| Nuva Ring® | 99.7%, 92% |
| Transdermal (Ortho Evra®) | 99.7%, 92% |
| Depo-Provera® | 99.7%, 97% |
| Progestin-only pill (Micronor®) | 90-99% |
| Mirena® IUS | 99.9% |
| Jaydess® IUS | 99.9% |
| **Copper IUD** | 99.3% |
| **Surgical** | |
| Tubal ligation | 99.65% |
| Vasectomy | 99.9% |
| **Emergency Postcoital Contraception (EPC)** | |
| Yuzpe® method | 98% (within 24 h), decreases by 30% at 72 h |
| "Plan B" levonorgestrel only | 98% (within 24 h), decreases by 70% at 72 h |
| Postcoital IUD | 99.9% |
| Ella | 98% (within 120 h) |

*Effectiveness: percentage of women reporting no pregnancy after 1 yr of use

**Counselling the Adolescent about Contraception**
More than 90% of adolescent pregnancies are unintended, and ~50% of all pregnancies occur within the first 6 mo of initiating sexual activity; in addition, 85% of sexually active women become pregnant within 1 yr if no contraception is used and even some of the least effective contraceptive methods markedly decrease the risk of pregnancy

**New Oral Contraceptive Preparations and the Risk of Venous Thromboembolism vs. Second Generation Drugs**
BMJ 2015;350:h2135
**Summary**: Risks of thromboembolism associated with combined OCPs were higher for drug preparations with newer progesterone types than for second generation drugs (levonorgestrel and noresthisterone) and norgestimate.
**Methods**: Two nested case-control studies were performed on UK population through two large databases containing total of 1340 practices. Women aged 15-49 years with a first diagnosis of VTE in 2001-13 were matched with five controls by age, practice, and calendar year. OR for VTE incidence and use of combined OCPs were adjusted for smoking status, alcohol consumption, ethnic group, BMI, comorbidities, and other contraceptive drugs.
**Results**: Current exposure to OCP was associated with adjusted OR of 2.97 (95% CI 2.78-3.17) compared to no exposure in previous year. Risks associated with current exposure to new progesterone drug preparations (desogestrel, gestodene, drospirenone, cyproterone) were significantly higher than those for second generation contraceptives (levonorgestrel, noresthisterone) and norgestimate.

# Hormonal Methods

## Combined Oral Contraceptive Pills

- progestin: prevents LH surge, suppresses ovulation, thickens cervical mucus, decreases tubal motility, decidualizes endometrium
- estrogen: suppresses FSH and follicular development, causes endometrial proliferation
- most contain low dose ethinyl estradiol (20-35 μg) plus progestin (norethinedrone, norgestrel, levonorgestrel, desogestrel, norgestimate, drospirenone)
- failure rate (0.3% to 8%) depending on compliance
- monophasic or triphasic formulations (varying amount of progestin throughout cycle)

## Transdermal (Ortho Evra®)

- continuous release of 6 mg norelgestromin and 0.60 mg ethinyl estradiol into bloodstream
- applied to lower abdomen, back, upper arm, buttocks, NOT breast
- worn for 3 consecutive weeks (changed every wk) with 1 wk off to allow for menstruation
- as effective as OCP in preventing pregnancy (>99% with perfect use)
- may be less effective in women >90 kg
- may not be covered by drug plans

## Contraceptive Ring (Nuva Ring®)

- thin flexible plastic ring; releases etonogestrel 120 μg/d and estradiol 15 μg/d
- works for 3 wk then removed for 1 wk to allow for menstruation
- as effective as OCP in preventing pregnancy (98%)
- side effects: vaginal infections/irritation, vaginal discharge
- may have better cycle control; i.e. decreased breakthrough bleeding

## Starting Hormonal Contraceptives

- thorough history and physical exam, including blood pressure and breast exam
- can start at any time during cycle but ideal if within 5 d of LMP
- follow-up visit 6 wk after hormonal contraceptives prescribed
- pelvic exam not required as STI screening can be done by urine and pap smear screening does not start until >21 yr

### Table 8. Combined Estrogen and Progestin Contraceptive Methods

| Advantages | Side Effects | Contraindications |
|---|---|---|
| Highly effective<br>Reversible<br>Cycle regulation<br>Decreased dysmenorrhea and heavy menstrual bleeding (less anemia)<br>Decreased benign breast disease and ovarian cyst development<br>Decreased risk of ovarian and endometrial cancer<br>Increased cervical mucus which may lower risk of STIs<br>Decreased PMS symptoms<br>Improved acne<br>Osteoporosis protection (possibly) | **Estrogen-related**<br>Nausea<br>Breast changes (tenderness, enlargement)<br>Fluid retention/bloating/edema<br>Weight gain (rare)<br>Migraine, headaches<br>Thromboembolic events<br>Liver adenoma (rare)<br>Breakthrough bleeding (low estradiol levels)<br><br>**Progestin-related**<br>Amenorrhea/breakthrough bleeding<br>Headaches<br>Breast tenderness<br>Increased appetite<br>Decreased libido<br>Mood changes<br>HTN<br>Acne/oily skin*<br>Hirsutism*<br><br>* Androgenic side effects may be minimized by prescribing formulations containing desogestrel, norgestimate, drospirenone, or cyproterone acetate | **Absolute**<br>Known/suspected pregnancy<br>Undiagnosed abnormal vaginal bleeding<br>Prior thromboembolic events, thromboembolic disorders (Factor V Leiden mutation; protein C or S, or antithrombin III deficiency), active thrombophlebitis<br>Cerebrovascular or coronary artery disease<br>Estrogen-dependent tumours (breast, uterus)<br>Impaired liver function associated with acute liver disease<br>Congenital hypertriglyceridemia<br>Smoker age >35 yr<br>Migraines with focal neurological symptoms (excluding aura)<br>Uncontrolled HTN<br><br>**Relative**<br>Migraines (non-focal with aura <1 h)<br>DM complicated by vascular disease<br>SLE<br>Controlled HTN<br>Hyperlipidemia<br>Sickle cell anemia<br>Gallbladder disease<br><br>**Drug Interactions/Risks**<br>Rifampin, phenobarbital, phenytoin, griseofulvin, primidone, and St. John's wort can decrease efficacy, requiring use of back-up method<br>No evidence of fetal abnormalities if conceived on OCP<br>No evidence that OCP is harmful to nursing infant but may decrease milk production; not recommended until 6 wk postpartum in breastfeeding and non-breastfeeding moms, ideally ≥3 mo postpartum if BF |

### Table 9. Selected Examples of OCPs

| Type | Active Compounds (estriol and progestin derivative) | Advantages | Disadvantages |
|---|---|---|---|
| **Alesse®** | 20 µg ethinyl estradiol and 0.5 mg levonorgestrel | Low dose (20 µg) OCP<br>Less estrogen side effects | Low-dose pills can often result in breakthrough bleeding<br>If this persists for longer than 3 mo, patient should be switched to an OCP with higher estrogen content |
| **Tri-cyclen®** | 35 µg ethinyl estradiol and 0.180/0.215/0.250 mg norgestimate<br>Triphasic oral contraceptive (graduated levels of progesterone) | Low androgenic activity can help with acne | Triphasic OCPs not ideal for continuous use >3 wk in a row (unlike monophasic formulation) |
| **Yasmin® and Yaz®** | Yasmin®: 30 µg ethinyl estradiol + 3 mg drospirenone (a new progestin)<br>Yaz®: 20 µg ethinyl estradiol + 3 mg drospirenone – 24/4-d pill (4 d pill free interval)<br>Drospirenone has antimineralocorticoid activity and antiandrogenic effects | Decreased perception of cyclic weight gain/bloating<br>Fewer PMS symptoms<br>Improved acne | Hyperkalemia (rare, contraindicated in renal and adrenal insufficiency)<br>Check potassium if patient also on ACEI, ARB, K⁺-sparing diuretic, heparin<br>Continue use of spironolactone |

Irregular breakthrough bleeding often occurs in the first few months after starting OCP; usually resolves after three cycles

Progestin only contraceptives must be taken at the same time every day

**Missed Combined OCPs**

**Miss 1 pill in <24 h**
- Take 1 pill ASAP, and the next pill at the usual time

**Miss ≥1 pill in a row in 1st wk**
- Take 1 pill ASAP, and continue taking one pill daily until the end of the pack
- Use back-up contraception for 7 d; EPC may be necessary

**Miss <3 pills in 2nd or 3rd wk of cycle**
- Take 1 pill ASAP, and continue taking one pill daily until the end of the pack
- Do not take placebo (28-d packs) or do not take a hormone free interval (21-d packs)
- Start the next pack immediately after finishing the previous one
- No need for back-up contraception

**Miss ≥3 pills during the 2nd or 3rd wk**
- Take 1 pill ASAP, and continue taking one pill daily until the end of the pack
- Do ot take placebo (28-d packs) or do not take a hormone free interval (21-d packs)
- Start the next pack immediately after finishing the previous one
- Use back-up contraception for 7 d; EPC may be necessary

SOGC Committee Opinion on Missed Hormonal Contraceptives: New Recommendations. *JOGC* 2008;30:1050-1062. http://www.sogc.org/guidelines/documents/gui219ECO0811.pdf

## PROGESTIN-ONLY METHOD

### Table 10. Progestin Only Contraceptive Methods

| Indications | Mechanism of Action | Side Effects | Contraindications |
|---|---|---|---|
| Suitable for postpartum women (does not affect breast milk supply)<br>Women with contraindications to combined OCP (e.g. thromboembolic or myocardial disease)<br>Women intolerant of estrogenic side effects of combined OCPs | Progestin prevents LH surge<br>Thickening of cervical mucus<br>Decrease tubal motility<br>Endometrial decidualization<br>Ovulation suppression – oral progestins (not IM) do not consistently suppress compared to combined OCPs | Irregular menstrual bleeding<br>Weight gain<br>Headache<br>Breast tenderness<br>Mood changes<br>Functional ovarian cysts<br>Acne/oily skin<br>Hirsutism | **Absolute**<br>None |

## SELECTED EXAMPLES OF PROGESTIN-ONLY METHODS

### Progestin-Only Pill ("minipill")

- Micronor® 0.35 mg norethindrone
- must be taken daily at same time of day to ensure reliable effect; no pill free interval
- higher failure rate (1.1-13% with typical use, 0.51% with perfect use) than other hormonal methods
- ovulation inhibited only in 60% of women; most have regular cycles (but may cause oligo/amenorrhea)
- highly effective if also post-partum breastfeeding, or if >35 yr
- relies on the progestin effects on the cervical mucous and endometrial lining

### Depo-Provera®

- injectable depot medroxyprogesterone acetate
- dose 150 mg IM q12-14wk (convenient dosing)
- initiate ideally within 5 d of beginning of normal menses, immediately postpartum in breastfeeding and non-breastfeeding women. Can consider quick start
- irregular spotting progresses to complete amenorrhea in 70% of women (after 1-2 yr of use)
- highly effective 99%; failure rate 0.3%
- suppresses ovulation very effectively
- side effect: decreased bone density (may be reversible) and weight gain
- disadvantage: restoration of fertility may take up to 9 mo

**Missed Progestin-Only Pills >3 h**
Use back-up contraceptive method for at least 48 h; continue to take remainder of pills as prescribed

**Missed Depo-Provera**

- If last injection given 13-14 wk prior: give next injection immediately
- If >14 wk prior, do β-hCG
  - If β-hCG is positive, give EPC and no injection
  - If β-hCG is negative, give next injection right away and:
    - Intercourse occurred in last 5 d: give EPC, use back-up contraception for 7 d ; repeat β-hCG in 3 wk
    - Intercourse occurred >5 d ago but within the last 14 d: use back-up contraception for 7 d; repeat β-hCG in 3 wk
    - Intercourse occurred >14 d ago: use back-up contraception for 7 d
  - No evidence of fetal abnormalities if conceived on DMPA

SOGC Committee Opinion on Missed Hormonal Contraceptives: New Recommendations.
*JOGC* 2008;30:1050-62. http://www.sogc.org/guidelines/documents/gui219ECO0811.pdf

# Intrauterine Device

**Table 11. IUS/IUD Contraceptive Methods**

| Mechanism of Action | Side Effects | Contraindications |
|---|---|---|
| **Copper-Containing IUD (Nova-T®):** mild foreign body reaction in endometrium; toxic to sperm and alters sperm motility<br><br>**Progesterone-Releasing IUS (MirenaV, Kyleena®, Jaydess®):** decidualization of endometrium and thickening of cervical mucus; minimal effect on ovulation<br><br>Highly effective (95-99%); failure rate 0-1.2%<br>Contraceptive effects last 5 yr<br>Reversible, private, convenient<br>May be used in women with contraindications to OCPs or wanting long-term contraception | **Both Copper and Progesterone IUD**<br>Breakthrough bleeding<br>Expulsion (5% in the 1st yr, greatest in 1st mo and in nulliparous women)<br>Uterine wall perforation (1/1000) on insertion<br>If pregnancy occurs with an IUD, increased risk of ectopic<br>Increased risk of PID (within first 10 d of insertion only)<br><br>**Copper IUD:** increased blood loss and duration of menses, dysmenorrhea<br><br>**Progesterone IUD:** bloating, headache | **Absolute**<br>**Both Copper and Progesterone IUD**<br>Known or suspected pregnancy<br>Undiagnosed genital tract bleeding<br>Acute or chronic PID<br>Lifestyle risk for STIs*<br><br>**Copper IUD**<br>Known allergy to copper<br>Wilson's disease<br><br>**Relative**<br>**Both Copper and Progesterone IUD**<br>Valvular heart disease<br>Past history of PID or ectopic pregnancy<br>Presence of prosthesis<br>Abnormalities of uterine cavity, intracavitary fibroids<br>Cervical stenosis<br>Immunosuppressed individuals (e.g. HIV)<br>**Copper IUD**<br>Severe dysmenorrhea or heavy menstrual bleeding |

*Cervical swabs for gonorrhea and chlamydia should be done prior to insertion

**Continuous or Extended Cycle vs. Cyclic Use of Combined Hormonal Contraceptives for Contraception**
Cochrane DB Syst Rev 2014:7
**Purpose**: Systematic review of RCTs assessing the efficacy and side effects of cyclic administration vs. extended use (longer periods of active pills and/or shorter periods placebo) or continuous use (uninterrupted active pill administration) of combination oral contraceptives (COC).
**Results**: The initial review published in 2012 identified 12 RCTs that ultimately showed no difference between groups with regards to efficacy (pregnancy rates), safety, and compliance rates. Continuous or extended CHCs were shown to reduce menstrual symptoms (headaches, tiredness, bloating, and menstrual pain). In addition, 11 of 12 studies reported similar or improved bleeding patterns with continuous or extended cycles.
**Conclusions**: This recently published updated systematic review identified a further 4 RCTs, however, results did not change.

**Committee Opinion No. 602: Depot Medroxyprogresterone Acetate and Bone Effects**
Obstet Gynecol 2014(6):1298-402

- The effect of DMPA on BMD should neither prevent practitioners from prescribing DMPA nor limit its use to 2 consecutive yr.
- BMD loss due to DMPA appears to be substantially or fully reversible.
- Contraceptive implants and intrauterine devices that do not affect BMD should be considered as first-line for adolescents.
- Inform patients about benefits and the potential risks of DMPA, and encourage daily exercise, calcium and vitamin D intake.
- Routine BMD monitoring is not recommended for DMPA users.

# Emergency Postcoital Contraception

**Table 12. Emergency Contraceptive Methods**

| Method | Mechanism of Action | Side Effects | Contraindications |
|---|---|---|---|
| **HORMONAL** | | | |
| **Yuzpe Method**<br>Used within 72 h of unprotected intercourse; limited evidence of benefit up to 5 d<br>Ovral® 2 tablets then repeat in 12 h (ethinyl estradiol 100 µg/ levonorgestrel 500 µg)<br>Can substitute with any OCP as long as same dose of estrogen used<br>2% overall risk of pregnancy<br>Efficacy decreased with time (e.g. less effective at 72 h than 24 h) | Unknown; theories include:<br>Suppresses ovulation or causes deficient luteal phase<br>Alters endometrium to prevent implantation<br>Affects sperm/ova transport | Nausea (due to estrogen; treat with Gravol®)<br>Irregular spotting | Pre-existing pregnancy (although not teratogenic)<br>Caution in women with contraindications to OCP (although NO absolute contraindications) |
| **"Plan B"**<br>Consists of levonorgestrel 750 µg q12h for 2 doses (can also take 2 doses together); taken within 72 h of intercourse. Can be taken up to 5 d<br>Greater efficacy (75-95% if used within 24 h) and better side effect profile than Yuzpe method but efficacy decreases with time; 1st line if >24 h<br>No estrogen thus very few contraindications/side effects (less nausea)<br>Less effective in overweight individuals (>75 kg less effective, >80 kg not recommended) | Same as above | Same as above | Same as above but no caution in women with contraindications to OCP |
| **Ulipristal**<br>30 mg PO within 5 d | Selective Progesterone Receptor Modulator (SPERM) with primarily antiprogestin activity: may delay ovulation by up to 5 d | Headache, hot flashes, constipation, vertigo, endometrial thickening | Same as above but no caution in women with contraindications to OCP |
| **NON-HORMONAL** | | | |
| **Postcoital IUD (Copper)**<br>Insert up to 7 d postcoitus<br>Prevents implantation<br>1% failure rate<br>Can use for short duration in higher risk individuals<br>Mirena® IUS cannot be used as EPC | See Table 11 | See Table 11 | See Table 11 |

## Follow-up

- 3-4 wk post treatment to confirm efficacy (confirmed by spontaneous menses or pregnancy test)
- contraception counselling

# Termination of Pregnancy

There is no association between termination of pregnancy and either future breast cancer or future development of psychiatric disease

## Indications

- patient desires an end to pregnancy
- may be for medical reasons (mother or fetus unhealthy) or social reasons, including patient request

## Legal Issues

- no current law in Canada concerning abortion therefore considered legal at any gestational age
- CPSO: a physician must refer for abortion services regardless of personal beliefs, but not compelled to perform procedure

## Rates

- 13.1 abortions/1000 women aged 15-44 in Canada (2017 CIHI data)
- worldwide: 42 million induced abortions per year; half are unsafe (WHO data)
- maternal mortality almost zero where induced abortion is safe and legal; rises to 100 maternal deaths/100,000 live births in sub-Saharan Africa and other countries where abortion is illegal and unsafe
- in Canada, 91% of induced abortions occur <12 wk GA; very rare after 24 wk (usually only for maternal/fetal reasons)

## Methods of induced abortion

- medical
  - gold standard up to 9 wk GA: mifepristone and misprostol : 95-98% effective
  - mifepristone blocks the progesterone receptor (progesterone required in early pregnancy)
  - misoprostol induces uterine contractions
  - can also use misoprostol alone or methotrexate and misoprostol (with lower success rates of 90-95%)
  - side effects: bleeding (self-limited) and pain (while tissue passes) are expected side effects

- surgical
  - <14 wk:
    - manual vacuum aspiration – up to about 8-9 wk with hand held aspiration device
    - suction dilatation + aspiration ± curettage – may involve pre-surgical preparation of cervix with laminaria tents and/or misoprostol
  - 14-24 wk: dilatation and evacuation; pre- surgical preparation of cervix required with laminaria tents
  - pain or discomfort during procedure mitigated by use of appropriate analgesia/sedation/anesthesia (including paracervical blocks)
  - rare complications (1-5%): laceration of cervix, infection/endometritis, retained products of conception, ongoing pregnancy
  - very rare complications: (0.1-2%) : hemorrhage, perforation of uterus, Asherman's syndrome (adhesions within the endometrial cavity causing amenorrhea/infertility), future preterm birth (controversial and likely only with repeated abortion)
- counselling
  - options counselling always provided; always offer possibility of carrying pregnancy with/without adoption
  - offer future contraception and family planning services
  - ensure follow-up

# Pregnancy-Related Complications

## First and Second Trimester Bleeding

### Approach to the Patient with Bleeding in T1/T2

#### History
- risk factors for ectopic pregnancy (see *Ectopic Pregnancy*, GY20)
- previous spontaneous abortion
- recent trauma
- characteristics of the bleeding (including any tissue passed)
- characteristics of the pain (cramping pain suggests spontaneous abortion)
- history of coagulopathy
- gynecological/obstetric history
- fatigue, dizziness, syncopal episodes due to hypovolemia, fever (may be associated with septic abortion)

#### Physical
- vitals (including orthostatic changes)
- abdomen (symphysis fundal height, tenderness, presence of contractions)
- perineum (signs of trauma, genital lesions)
- speculum exam (cervical os open or closed, presence of active bleeding/clots/tissue)
- pelvic exam (uterine size, adnexal mass, uterine/adnexal tenderness, cervical motion tenderness)

#### Investigations
- β-hCG (may be lower than expected for GA in spontaneous abortion, can be used to diagnose viable pregnancy vs. ectopic pregnancy vs. abortion)
- U/S (confirm intrauterine pregnancy and fetal viability)
- CBC
- group and screen

#### Treatment
- IV resuscitation for hemorrhagic shock
- treat the underlying cause



**Bleeding in Pregnancy Definitions**
- First trimester bleeding: vaginal bleeding within the first 12 wk
- Second trimester bleeding: 12-20 wk



**Differential Diagnosis**
- Physiologic bleeding: spotting, due to implantation of placenta – reassure and check serial β-hCGs
- Abortion (threatened, inevitable, incomplete, complete)
- Abnormal pregnancy (ectopic, molar) (see *Hydatidiform Mole*, GY49)
- Trauma (post-coital or after pelvic exam)
- Genital lesion (e.g. cervical polyp, neoplasms)
- Subchorionic hematoma



Every woman of childbearing age presenting to ER with abdominal or pelvic pain should have β-hCG measured

# Spontaneous Abortions

- see *Termination of Pregnancy* for therapeutic abortions, GY18

**Table 13. Classification of Spontaneous Abortions**

| Type | History | Clinical | Management (± Rhogam®) |
|---|---|---|---|
| **Threatened** | Vaginal bleeding ± cramping | Cervix closed and soft | Watch and wait<br><5% go on to abort |
| **Inevitable** | Increasing bleeding and cramps ± rupture of membranes | Cervix closed until products start to expel, then external os opens | a) Watch and wait<br>b) Mifepristone 200 mg PO followed by Misoprostol 800 µg PV 24 h later<br>c) D&C |
| **Incomplete** | Extremely heavy bleeding and cramps ± passage of tissue noticed | Cervix open | a) Watch and wait<br>b) Mifepristone 200 mg PO followed by Misoprostol 800 µg PV 24 h later<br>c) D&C |
| **Complete** | Bleeding and complete passage of sac and placenta | Cervix closed, bleeding stopped | No D&C – expectant management |
| **Missed** | No bleeding (fetal death in utero) | Cervix closed | a) Watch and wait<br>b) Mifepristone 200 mg PO followed by Misoprostol 800 µg PV 24 h later<br>c) D&C |
| **Recurrent** | ≥3 consecutive spontaneous abortions | | Evaluate mechanical, genetic, environmental, and other risk factors |
| **Septic** | Contents of uterus infected – infrequent | | IV broad spectrum antibiotics and prompt uterine evacuation |

Embryonic demise can be diagnosed by ultrasound based on an intrauterine gestational sac, embryonic crown-rump length ≥7 mm, and no cardiac activity

# Ectopic Pregnancy

## Definition

- embryo implants outside of the endometrial cavity

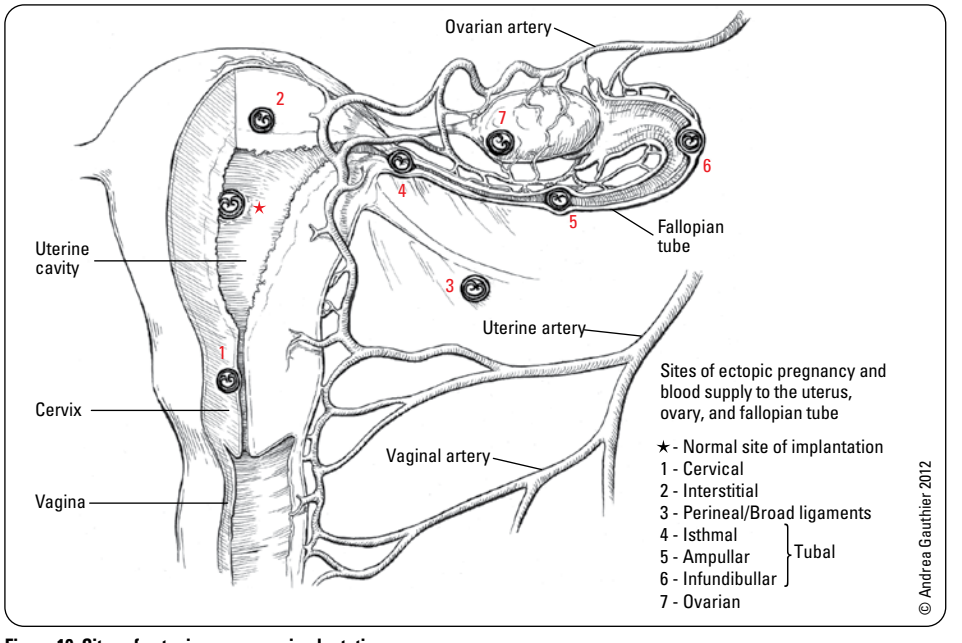



**Figure 10. Sites of ectopic pregnancy implantation**
ampullary (70%) >> isthmal (12%) > fimbrial (11%) > ovarian (3%) > interstitial (2%) > abdominal (1%)

## Epidemiology

- 1/100 pregnancies
- fourth leading cause of maternal mortality, leading cause of maternal death in first trimester
- increase in incidence over the last 3 decades
- three commonest locations for ectopic pregnancy: ampullary (70%), isthmic (12%), fimbrial (11%)

## Etiology

- 50% due to damage of fallopian tube cilia following PID
- intrinsic abnormality of the fertilized ovum
- conception late in cycle
- transmigration of fertilized ovum to contralateral tube

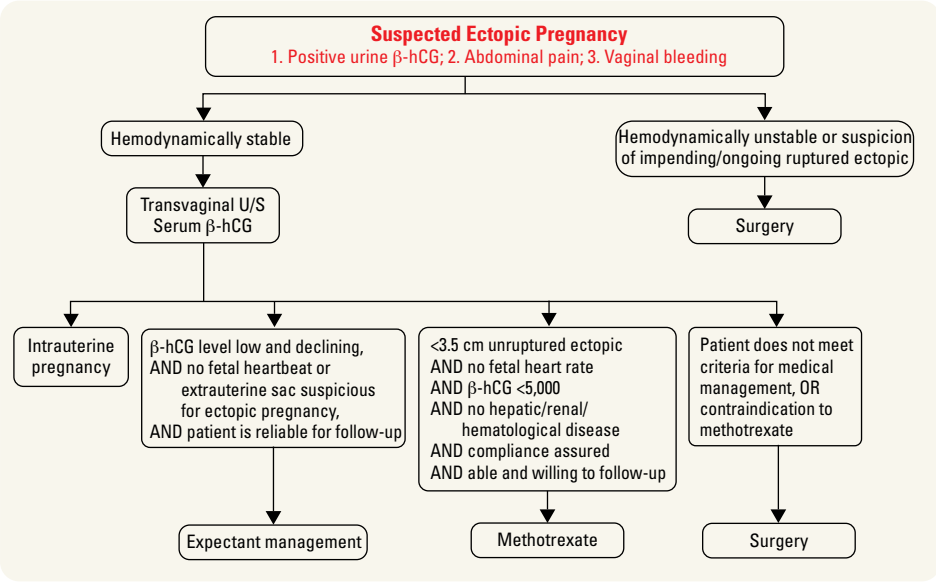



**Figure 11. Algorithm for suspected ectopic pregnancy**

## Risk Factors

- previous ectopic pregnancy
- gynecologic
  - current IUD use – increased risk of ectopic if pregnancy occurs
  - history of PID (especially infection with *C. trachomatis*), salpingitis
  - infertility
- infertility treatment (IVF pregnancies following ovulation induction (7% ectopic rate))
- previous procedures
  - any surgery on fallopian tube (for previous ectopic, tubal ligation, etc.)
  - abdominal surgery for ruptured appendix, etc.
- smoking
- structural
  - uterine leiomyomas
  - adhesions
  - abnormal uterine anatomy (e.g. T-shaped uterus)

## Investigations

- serial β-hCG levels; normal doubling time with intrauterine pregnancy is 1.6-2.4 d in early pregnancy
  - rise of <20% of β-hCG (1.6-2.4 d) is 100% predictive of a non-viable pregnancy
  - prolonged doubling time, plateau, or decreasing levels before 8 wk implies nonviable gestation but does not provide information on location of implantation
  - 85% of ectopic pregnancies demonstrate abnormal β-hCG doubling
- ultrasound
  - U/S is only definitive if fetal cardiac activity is detected in the tube or uterus
  - specific finding on transvaginal U/S is a tubal ring
- suspect ectopic in case of empty uterus by TVUS with β-hCG >2000-3000 mIU/ml
- laparoscopy (sometimes used for definitive diagnosis)

## Treatment

- goals of treatment: conservative (preserve tube if possible), maintain hemodynamic stability
- surgical = laparoscopy
  - linear salpingostomy an option if tube salvageable, however, patient must be reliable to follow-up with weekly β-hCG
  - salpingectomy if tube damaged or ectopic is ipsilateral recurrence
  - 15% risk of persistent trophoblast if salpingectomy; must monitor β-hCG titres weekly until they reach non-detectable levels
  - consider Rhogam® if Rh negative
  - patient may require laparotomy if unstable, extensive abdominal surgical history, etc.
- medical = methotrexate
  - use 50 mg/m$^2$ body surface area; given in a single IM dose
  - this is 1/5 to 1/6 chemotherapy dose, therefore minimal side effects (reversible hepatic dysfunction, diarrhea, gastritis, dermatitis)
  - follow β-hCG levels weekly until β-hCG is non-detectable
    - plateaued or rising levels suggest persistent trophoblastic tissue requiring further treatment

**Contraindications to Methotrexate Therapy for Ectopic Pregnancy**

- Abnormalities in hematologic, hepatic or renal function
- Immunodeficiency
- Active pulmonary disease
- Peptic ulcer disease
- Hypersensitivity to methotrexate
- Heterotopic pregnancy with coexisting viable intrauterine pregnancy
- Breastfeeding
- Unwilling or unable to adhere to methotrexate protocol

**DDx of Lower Abdominal Pain**

- Urinary tract: UTI, kidney stones
- GI: diverticulitis, appendicitis
- Gyne: endometriosis, PID, fibroid (degenerating, infarcted, torsion), ovarian torsion, ovarian neoplasm, ovarian cyst, pregnancy-related

Any woman presenting with abdominal pain, vaginal bleeding and amenorrhea is an ectopic pregnancy until proven otherwise

More than half of patients with ectopic pregnancy have no risk factors

**Presentation of Ectopic Pregnancy Ruptures**

- Acute abdomen with increasing pain
- Abdominal distention
- Shock

**Management of Abortions**

- Always rule out an ectopic
- Always check Rh; if negative, give Rhogam®
- Always ensure patient is hemodynamically stable

  - 82-95% success rate, but up to 25% will require a second dose
    - administer a second dose if β-hCG does not decrease by at least 15% between days 4 and 7
  - tubal patency following methotrexate treatment approaches 80%
- expectant management is an option for patients who are clinically stable, reliable for follow-up, and have β-hCG levels that are low and declining

### Prognosis
- 9% of maternal deaths during pregnancy attributed to ectopic pregnancy
- 40-60% of patients will become pregnant again after surgery
- 10-20% will have subsequent ectopic pregnancy

# Infertility

### Epidemiology
- 10-15% of couples, must investigate both members of the couple

## Female Factors

### Etiology
- ovulatory dysfunction (15-20%)
  - hypothalamic (hypothalamic amenorrhea)
    - stress, poor nutrition, excessive exercise (even with presence of menstruation), history of eating disorders
  - pituitary (prolactinoma, hypopituitarism)
  - ovarian
    - PCOS
    - primary ovarian insufficiency
    - luteal phase defect (poor follicle production, premature corpus luteum failure, failed uterine lining response to progesterone), poorly understood
  - systemic diseases (thyroid, Cushing's syndrome, renal/hepatic failure), diabetes
  - congenital (Turner's syndrome, gonadal dysgenesis, or gonadotropin deficiency)
- outflow tract abnormality (15-20%)
  - tubal factors (20-30%)
    - PID
    - adhesions (previous surgery, peritonitis, endometriosis)
    - ligation/occlusion (e.g. previous ectopic pregnancy)
  - uterine factors (<5%)
    - congenital anomalies, bicornuate uterus, septate uterus, prenatal DES exposure, intrauterine adhesions (e.g. Asherman's syndrome), fibroids/polyps (particularly intrauterine)
    - infection (endometritis, pelvic tuberculosis)
    - endometrial ablation
  - cervical factors (5%)
    - hostile or acidic cervical mucus, anti-sperm antibodies
    - structural defects (cone biopsies, laser or cryotherapy)
- endometriosis (15-30%)
- multiple factors (30%)
- unknown factors (10-15%)

### Investigations
- ovulatory
  - day 3: FSH, LH, TSH, prolactin ± DHEA, free testosterone (if hirsute) add estradiol for proper FSH interpretation
  - day 21-23: serum progesterone to confirm ovulation
  - initiate basal body temperature monitoring (biphasic pattern)
  - postcoital test: evaluate mucus for clarity, pH, spinnbarkeit/fibrosity (rarely done)
- tubal factors
  - HSG (can be therapeutic – opens fallopian tube)
  - SHG (can be therapeutic; likely less – opens fallopian tube)
  - laparoscopy with dye insufflation (or tubal dye test) rarely done as diagnostic
- peritoneal/uterine factors
  - HSG/SHG, hysteroscopy
- other
  - karyotype

Infertility: inability to conceive or carry to term a pregnancy after one year of regular, unprotected intercourse
**Primary infertility**: infertility in the context of no prior pregnancies
**Secondary infertility**: infertility in the context of a prior conception
Generally, 75% of couples achieve pregnancy within 6 mo, 85% within 1 yr, 90% within 2 yr

**When Should Investigations Begin?**
- <35 yr: after 1 yr of regular unprotected intercourse
- 35-40 yr: after >6 mo
- >40 yr: immediately
- Earlier if
  - History of PID
  - History of infertility in previous relationship
  - Prior pelvic surgery
  - Chemotherapy/radiation in either partner
  - Recurrent pregnancy loss
- Moderate-severe endometriosis

**Ethical Considerations in Infertility Treatment**
- Infertility demands non-judgmental discussion
- Ethical issues surrounding therapeutic donor insemination in same sex couples, surrogacy, donor gametes, and other advanced reproductive technologies are still evolving and remain controversial
- If the doctor finds that certain treatment options lie outside of their moral boundaries, the infertile couple should be referred to another physician

### Treatment
- education: timing intercourse relative to ovulation (from 2 d prior to 2 d following presumed ovulation), every other day
- medical
  - ovulation induction
    - clomiphene citrate (Clomid®): estrogen antagonist causing a perceived decreased estrogen state, resulting in increased pituitary gonadotropins; which increases FSH and LH and induces ovulation (better results if anovulatory)
    - followed by β-hCG for stimulation of ovum release
    - Letrozole: aromatase inhibitor. May be associated with a higher rate of live births in patients with PCOS
  - may add:
    - bromocriptine (dopamine agonist) if elevated prolactin
    - dexamethasone for hyperandrogenism (adult onset congenital adrenal hyperplasia)
    - metformin (for PCOS)
    - luteal phase progesterone supplementation for luteal phase defect (mechanism not completely understood)
    - anticoagulation and ASA (81 mg PO OD) for women with a history of recurrent spontaneous abortions (for antiphospholipid antibody syndrome)
    - thyroid replacement to keep TSH <2.5
- surgical/procedural
  - tubuloplasty
  - lysis of adhesions
  - artificial insemination: intracervical insemination (ICI), intrauterine insemination (IUI), intrauterine tuboperitoneal insemination (IUTPI), intratubal insemination (ITI)
  - sperm washing
  - IVF ( fertilization)
  - IFT (intrafallopian transfer)
  - GIFT* (gamete intrafallopian transfer): immediate transfer with sperm after oocyte retrieval
  - ZIFT* (zygote intrafallopian transfer): transfer after 24 h culture of oocyte and sperm
  - TET* (tubal embryo transfer): transfer after >24 h culture
  - ICSI (intracytoplasmic sperm injection)
  - IVM (in vitro maturation)
  - ± oocyte or sperm donors
  - ± pre-genetic screening for single gene defects in karyotype of zygote

*not performed in Canada

# Male Factors

- see Urology, U36

### Etiology
- varicocele (>40%)
- idiopathic (>20%)
- obstruction (~15%)
- cryptorchidism (~8%)
- immunologic (~3%)

### Investigations
- semen analysis and culture
- postcoital (Huhner) test: rarely done

**Normal Semen Analysis (WHO lower reference limits)**
- Must be obtained after 2-7 d of abstinence
  - Volume 1.5 cc
  - Count 15 million/cc
  - Vitality 58% live
  - Motility 32% progressive, 40% total (progressive + non-progressive)
- Morphology 4.0% normal

# Polycystic Ovarian Syndrome

- also called chronic ovarian androgenism

### Etiology

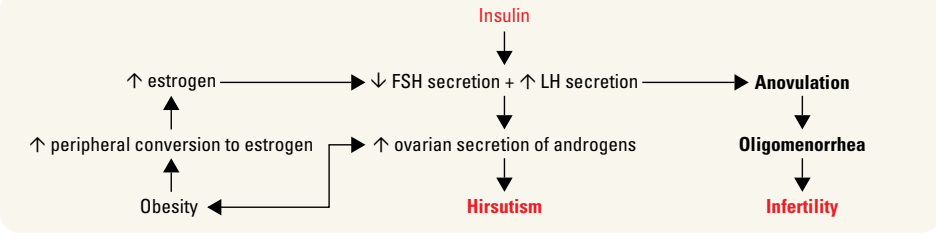



**Figure 12. Pathophysiology of polycystic ovarian syndrome**

**Polycystic Ovarian Syndrome – HAIR-AN**
**H**irsutism, **H**yper**A**ndrogenism, **I**nfertility, **I**nsulin **R**esistance, **A**canthosis **N**igricans

## Diagnosis

- Rotterdam diagnostic criteria: 2 of 3 required
  - oligomenorrhea/irregular menses for 6 mo
  - hyperandrogenism
    - clinical evidence - hirsutism or acne
    - biochemical evidence - raised free testosterone
  - polycystic ovaries on U/S (not appropriate in adolescents)

## Clinical Features

- average age 15-35 yr at presentation
- in adolescents, wait at least 1-2 yr to make diagnosis as adolescence resembles PCOS
- abnormal/irregular uterine bleeding, hirsutism, infertility, obesity, virilization
- acanthosis nigricans: browning of skin folds in intertriginous zones (indicative of insulin resistance)
- insulin resistance occurs in both lean and obese patients
- family history of DM

## Investigations

- goal: identify hyperandrogenism or chronic anovulation and rule out specific pituitary or adrenal disease as the cause
- laboratory
  - prolactin, 17-hydroxyprogesterone, free testosterone, DHEA-S, TSH, free T4, androstenedione, SHBG
  - LH:FSH >2:1; LH is chronically high with FSH mid-range or low (low sensitivity and specificity)
  - increased DHEA-S, androstenedione and free testosterone (most sensitive), decreased SHBG
- transvaginal or transabdominal U/S: polycystic-appearing ovaries ("string of pearls" – 12 or more small follicles 2-9 mm, or increased ovarian volume)
- tests for insulin resistance or glucose tolerance
  - fasting glucose:insulin ratio <4.5 is consistent with insulin resistance (U.S. units)
  - 75 g OGTT yearly (particularly if obese)
- laparoscopy
  - not required for diagnosis
  - most common to see white, smooth, sclerotic ovaries with a thick capsule; multiple follicular cysts in various stages of atresia; and hyperplastic theca and stroma
- rule out other causes of abnormal bleeding

## Treatment

- cycle control
  - lifestyle modification (decrease BMI, increase exercise) to decrease peripheral estrone formation
  - OCP monthly or cyclic Provera® to prevent endometrial hyperplasia due to unopposed estrogen
  - oral hypoglycemic (e.g. metformin) if type 2 diabetic or if trying to become pregnant
  - tranexamic acid (Cyklokapron®) for menorrhagia only
- infertility
  - medical induction of ovulation: letrozole, clomiphene citrate (no longer available in Canada), human menopausal gonadotropins (HMG [Pergonal®]), LHRH, recombinant FSH, and metformin
    - metformin may be used alone or in conjuction with clomiphene citrate for ovulation induction
  - ovarian drilling (perforate the stroma), wedge resection of the ovary
  - bromocriptine (if hyperprolactinemia)
- hirsutism
  - any OCP can be used
    - Diane 35® (cyproterone acetate): antiandrogenic
    - Yasmin® (drospirenone and ethinyl estradiol): spironolactone analogue (inhibits steroid receptors)
  - mechanical removal of hair
  - finasteride (5-α reductase inhibitor)
  - flutamide (androgen reuptake inhibitor)
  - spironolactone: androgen receptor inhibitor

**PCOS May be Confused with**

- Late onset congenital adrenal hyperplasia (21-hydroxylase deficiency)
- Cushing's syndrome
- Ovarian and adrenal neoplasms
- Hyperprolactinemia
- Hypothyroidism

**Clinical Signs of Endocrine Imbalance**

- Menstrual disorder/amenorrhea (80%)
- Infertility (74%)
- Hirsutism (69%)
- Obesity (49%)
- Impaired glucose tolerance (35%)
- DM (10%)

**Long-Term Health Consequences**

- Hyperlipidemia
- Adult-onset DM
- Endometrial hyperplasia
- Infertility
- Obesity
- Sleep apnea

**Insulin-Sensitising Drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for Women with Polycystic Ovary Syndrome, Oligo Amenorrhoea and Subfertility**

Cochrane Database Syst Rev 2012; (5):CD003053

**Purpose**: To evaluate efficacy of insulin-sensitising drugs in improving reproductive outcomes of women with PCOS.

**Methods**: 42 RCTs (n=3992) were included.

**Conclusions**: Metformin was associated with improved clinical pregnancy rates whether used alone or in combination with clomiphene. However, this did not translate into live birth rates.

**Diagnostic Criteria for Polycystic Ovary Syndrome: Pitfalls and Controversies**

JOGC 2008;8:671-679

At present, there is no clear-cut definition of biochemical hyperandrogenemia, particularly since there is dependence on poor laboratory standards for measuring androgens in women. Clinical signs of hyperandrogenism are ill-defined in women with PCOS, and diagnosis of both hirsutism and polycystic ovarian morphology remains subjective. There is also the inappropriate tendency to assign ovulatory status solely on basis of menstrual cycle history or poorly timed endocrine measurements. Therefore it is important as clinicians to recognize the multi-factorial and complex nature of PCOS and place this in the context of our present diagnostic limitations.

# Gynecological Infections

## Physiologic Discharge

- clear, white, flocculent, odourless discharge; pH 3.8-4.2
- smear contains epithelial cells, Lactobacilli
- increases with increased estrogen states: pregnancy, OCP, mid-cycle, PCOS, or premenarchal
- if increased in perimenopausal/postmenopausal woman, consider investigation for other effects of excess estrogen (e.g. endometrial cancer)

## Pruritus

- can be caused by physiologic discharge and cervical mucus production
- non-physiologic
  - genital tract infection
  - vulvovaginitis: candidiasis, trichomoniasis, BV, polymicrobial superficial infection
  - chlamydia, gonorrhea
  - pyosalpinx, salpingitis
  - genital tract inflammation (non-infectious)
  - local: chemical irritants, douches, sprays, foreign body, trauma, atrophic vaginitis, desquamative inflammatory vaginitis, focal vulvitis
  - neoplasia: vulvar, vaginal, cervical, endometrial
  - systemic: toxic shock syndrome, Crohn's disease, collagen disease, dermatologic (e.g. lichen sclerosis)
  - IUD, OCP (secondary to progesterone)

## Vulvovaginitis

### PREPUBERTAL VULVOVAGINITIS

- clinical features: irritation, pruritus, discharge, vulvar erythema, vaginal bleeding (specifically due to Group A Streptococci and Shigella)
- etiology
  - poor hygiene (proximity of anus to vagina)
  - foreign bodies (most commonly tissue paper)
  - irritation by perfumed soaps, chemicals, and tight clothing
  - localized skin disorders: lichen sclerosis, condyloma acuminata
  - trauma: accidental straddle injury, sexual abuse
  - infectious
    - pinworms
    - Candida (if using diapers or chronic antibiotics)
    - Group A streptococcus, *S. aureus* and *Shigella*
    - discovery of STI should raise suspicion of sexual abuse
  - other
    - polyps, tumour (ovarian malignancy)
    - psychosomatic vaginal complaints (specific to vaginal discharge)
    - endocrine abnormalities (specific to vaginal bleeding)
    - blood dyscrasia (specific to vaginal bleeding)
- investigations
  - vaginal swab for culture (specifically state that it is a pre-pubertal specimen)
  - pH, wet-mount, and KOH smear in prepubertal adults only
- treatment
  - enhanced hygiene and local measures (handwashing, white cotton underwear, no nylon tights, no tight fitting clothes, no sleeper pajamas, sitz baths, avoid bubble baths, use mild detergent, eliminate fabric softener, avoid prolonged exposure to wet bathing suits, urination with legs spread apart)
  - A&D® dermatological ointment (vitamin A/D) to protect vulvar skin
  - infectious: treat with antibiotics for organism identified

**Table 14. Other Common Causes of Vulvovaginitis in Prepubertal Girls**

| | Pinworms | Lichen Sclerosis | Foreign Body |
|---|---|---|---|
| **Diagnosis** | Cellophane tape test | Area of white patches and thinning of skin (figure of 8) | |
| **Treatment** | Empirical treatment with mebendazole | Topical steroid creams | Irrigation of vagina with saline, may require local anesthesia or an exam under anesthesia |

**Vulvovaginitis**
Vulvar and vaginal inflammation

**Prepubertal and Adolescent Gynecological Infections: Legal Aspects of Confidentiality**
- Clinicians who treat adolescents must be aware of federal, state, and provincial laws related to adolescent consent and confidentiality
- Cllinicians must be aware of guidelines governing funding sources for particular services and be familiar with the consent and confidentiality policies of the facility in which they practice

There is no high quality evidence showing a link between vulvovaginal candidiasis and hygienic habits or wearing tight or synthetic clothing

Most common gynecological problem in prepubertal girls is non-specific vulvovaginitis, not yeast

## INFECTIOUS VULVOVAGINITIS

**Table 15. Infectious Vulvovaginitis**

| | Candidasis | Bacterial Vaginosis (BV) | Trichomoniasis |
|---|---|---|---|
| **Organisms** | *Candida albicans* (90%)<br>*Candida glabrata* (<5%)<br>*Candida tropicalis* (<5%) | *Gardnerella vaginalis*<br>*Mycoplasma hominis*<br>Anaerobes: *Prevotella, Mobiluncus, Bacteroides* | *Trichomonas vaginalis* (flagellated protozoan) |
| **Pathophysiology or Transmission** | Predisposing factors include:<br>Immunosuppressed host (DM, AIDS, etc.)<br>Recent antibiotic use<br>Increased estrogen levels (e.g. pregnancy, OCP) | Replacement of vaginal *Lactobacillus* with organisms above | Sexual transmission |
| **Discharge** | Whitish, "cottage cheese," minimal | Grey, thin, diffuse | Yellow-green, malodourous, diffuse, frothy |
| **Other** | 20% asymptomatic | 50-75% asymptomatic | 25% asymptomatic |
| **Signs/Symptoms** | Intense pruritus<br>Swollen, inflamed genitals<br>Vulvar burning, dysuria, dyspareunia | Fishy odour, especially after coitus<br>Absence of vulvar/vaginal irritation | Petechiae on vagina and cervix<br>Occasionally irritated, tender vulva<br>Dysuria, frequency |
| **pH** | ≤4.5 | ≥4.5 | ≥4.5 |
| **Saline Wetmount** | KOH wetmount reveals hyphae and spores | >20% clue cells = squamous epithelial cells dotted with coccobacilli (*Gardnerella*)<br>Paucity of WBC<br>Paucity of *Lactobacilli*<br>Positive whiff test: fishy odour with addition of KOH to slide (due to formation of amines) | Motile flagellated organisms<br>Many WBC<br>Inflammatory cells (PMNs)<br>Can have positive whiff test |
| **Treatment** | Clotrimazole, butoconazole, miconazole, terconazole suppositories, and/or creams for 1, 3, or 7 d treatments<br>Treatment in pregnancy is usually topical<br>Fluconazole 150 mg PO in single dose (can be used in pregnancy) | No treatment if non-pregnant and asymptomatic, unless scheduled for pelvic surgery or procedure<br>**Oral**<br>Metronidazole 500 mg PO bid x 7 d<br>**Topical**<br>Metronidazole gel 0.75% x 5 d OD (may be used in pregnancy)<br>Clindamycin 2% 5 g intravaginally at bedtime for 7 d<br>Probiotics (*Lactobacillus* sp.): oral or topical alone or as adjuvant | Treat even if asymptomatic<br>Metronidazole 2 g PO single dose or 500 mg bid x 7 d (alternative)<br>Symptomatic pregnant women should be treated with 2 g metronidazole once |
| **Other** | Prophylaxis for recurrent infection includes boric acid, vaginal suppositories, luteal phase fluconazole<br>Routine treatment of partner(s) not recommended (not sexually transmitted) | Associated with recurrent preterm labour, preterm birth, and postpartum endometritis<br>Need to warn patients on metronidazole not to consume alcohol (disulfiram-like action)<br>Routine treatment of partner(s) not recommended (not sexually transmitted) | Warnings accompanying metronidazole use<br>Treat partner(s) (sexually transmitted) |

# Sexually Transmitted Infections

• see Family Medicine, FM42

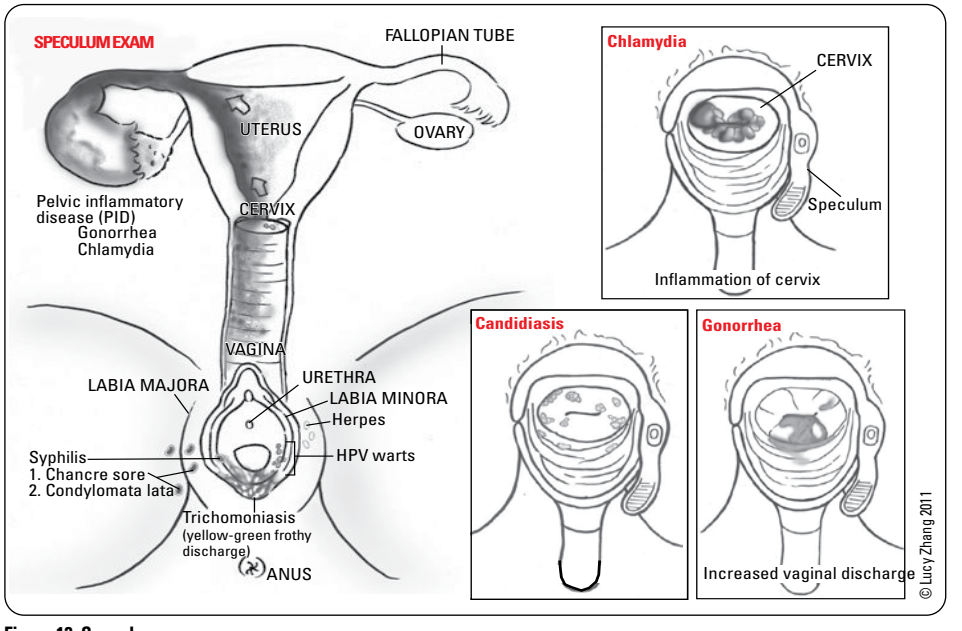



**Figure 13. Speculum exam**

**CDC Notifiable Diseases**
- Chancroid
- Chlamydia
- Gonorrhea
- Hepatitis A, B, C
- HIV
- Syphilis

**Risk Factors for STIs**
- History of previous STI
- Contact with infected person
- Sexually active individual <25 yr
- Multiple partners
- New partner in last 3 mo
- Lack of barrier protection use
- Street involvement (homelessness, drug use)

## TRICHOMONIASIS
- see *Infectious Vulvovaginitis*

## CHLAMYDIA

### Etiology
- Chlamydia trachomatis

### Epidemiology
- most common bacterial STI in Canada
- often associated with *N. gonorrhoeae*

### Clinical Features
- asymptomatic (80% of women)
- muco-purulent endocervical discharge
- urethral syndrome: dysuria, frequency, pyuria, no bacteria on culture
- pelvic pain
- postcoital bleeding or intermenstrual bleeding (particularly if on OCP and prior history of good cycle control)
- symptomatic sexual partner

### Investigations
- cervical culture or nucleic acid amplification test (can present in pharynx, rectum)
- obligate intracellular parasite: tissue culture is the definitive standard
- urine and self vaginal tests now available, which are equally or more effective than cervical culture



**STI Testing**
- Vaginal swab
  - Tests for bacterial vaginosis, trichomoniasis, candida
- Cervical swab
  - Tests for gonorrhea and chlamydia

### Treatment
- doxycycline 100 mg PO bid for 7 d or azithromycin 1 g PO in a single dose. Doxycycline is contra-indictated in the 2nd and 3rd trimesters of pregnancy
- also treat gonorrhea because of high rate of co-infection
- reportable disease, partners should also be referred for treatment
- test of cure for chlamydia required in pregnancy (cure rates lower in pregnant patients) → retest 3-4 wk after initiation of therapy

### Screening
- high-risk groups
- during pregnancy
- when initiating OCP if sexually active (independent risk factor)



Test of cure for *C. trachomatis* and *N. gonorrhoeae* is not routinely indicated
Repeat testing if symptomatic, if compliance with treatment is uncertain, or if pregnant

### Complications
- PID: low-grade salpingitis and adhesions resulting in tubal obstruction
- infertility
- ectopic pregnancy
- chronic pelvic pain
- Fitz-Hugh-Curtis syndrome (liver capsule inflammation)
- reactive arthritis (male predominance, HLA-B27 associated), conjunctivitis, urethritis
- perinatal infection: conjunctivitis, pneumonia

## GONORRHEA

### Etiology
- Neisseria gonorrhoeae
- symptoms and risk factors same as chlamydia

### Investigations
- Gram stain shows Gram-negative intracellular diplococci
- cervical, rectal, and throat culture (if clinically indicated)

### Treatment
- single dose of ceftriaxone 250 mg IM plus azithromycin 1 g PO
  - if pregnant: above regimen or 2 g spectinomycin IM plus azithromycin 1 g PO (avoid quinolones)
  - also treat chlamydia, due to high rate of co-infection
- treat partners
  - reportable disease
  - screening as with chlamydia

## HUMAN PAPILLOMAVIRUS

### Etiology
- most common viral STI in Canada
- >200 subtypes, of which >30 are genital subtypes
- HPV types 6 and 11 are classically associated with anogenital warts/condylomata acuminata
- HPV types 16 and 18 are the most oncogenic (classically associated with cervical HSIL)
- types 16, 18, 31, 33, 35, 36, 45 (and others) associated with increased incidence of cervical and vulvar intraepithelial hyperplasia and carcinoma

### Clinical Features
- latent infection
  - no visible lesions, asymptomatic
  - only detected by DNA hybridization tests
- subclinical infection
  - visible lesion found during colposcopy or on Pap test
- clinical infection
  - visible wart-like lesion without magnification (check pharynx too)
  - hyperkeratotic, verrucous or flat, macular lesions
  - vulvar edema

### Investigations
- cytology
- koilocytosis: nuclear enlargement and atypia with perinuclear halo
- biopsy of lesions at colposcopy
- detection of HPV DNA subtype using nucleic acid probes (not routinely done but can be done in presence of abnormal Pap test to guide treatment)

### Treatment
- patient administered
  - podofilox 0.5% solution or gel bid x 3 d in a row (4 d off) then repeat x 4 wk
  - imiquimod (Aldara®) 5% cream 3x/wk qhs x 16 wk
- provider administered
  - cryotherapy with liquid nitrogen: repeat q1-2wk
  - podophyllin resin in tincture of benzoin: weekly
  - trichloroacetic acid (TCA) (80-90%) or bichloroacetic acid weekly x 4-6 wk; safe in pregnancy
  - surgical removal/laser
  - intralesional interferon

### Prevention
- vaccination: Gardasil®9, Gardasil®, Cervarix® (see Table 28, GY45)
- condoms may not fully protect (areas not covered, must be used every time throughout entire sexual act)

## HERPES SIMPLEX VIRUS OF VULVA

### Etiology
- 90% are HSV-2, 10% are HSV-1

### Clinical Features
- may be asymptomatic
- initial symptoms: present 2-21 d after contact
- prodromal symptoms: tingling, burning, pruritus
- multiple, painful, shallow ulcerations with small vesicles appear 7-10 d after initial infection (absent in many infected persons); lesions are infectious
- inguinal lymphadenopathy, malaise, and fever often with first infection
- dysuria and urinary retention if urethral mucosa affected
- recurrent infections: less severe, less frequent, and shorter in duration (usually only HSV-2)

### Investigations
- viral culture preferred in patients with ulcer present; however decreased sensitivity as lesions heal
- cytologic smear (Tzanck smear) shows multinucleated giant cells, acidophilic intranuclear inclusion bodies
- HSV DNA PCR
- type specific serologic tests for antibodies to HSV-1 and HSV-2 (not available routinely in Canada)

**Genital Warts During Pregnancy**
- Condyloma tend to get larger in pregnancy and should be treated early (consider excision)
- C-section only if obstructing birth canal or risk of extensive bleeding
- Do not use imiquimod, podophyllin, or podofilox

**Human Rights in Health Equity: Cervical Cancer and HPV Vaccines**
Am J Law Med 2009;35:365-87
- While cervical cancer rates have drastically fallen in developed countries due to effective prevention and treatment, socially disadvantaged women within these countries remain disproportionately more likely to develop and die of cervical cancer.
- In most developing countries cervical cancer rates have risen or remained unchanged.
- Must recognize that cervical cancer disparities between race groups, urban and rural residence, and high and low socioeconomic status are attributed to disparate screening and vaccination coverage.
- Programs are implemented without sufficient attention to conditions that render screening less effective or inaccessible to disadvantaged social groups including: lack of information, undervaluing of preventive care, opportunistic delivery in limited health care settings, sexual health stigma, and related [illegible] concerns.

**A 9-Valent HPV Vaccine Against Infection and Intraepithelial Neoplasia in Women**
NEJM 2015;372:711-23
**Purpose**: To determine the efficacy and immunogenicity of the qHPV (types 6, 11, 16, 18) vs. 9vHPV (five additional types 31, 33, 45, 52, 58) vaccines.
**Method**: International randomized, double-blinded phase 2B-3 study of 9vHPV vaccine in 14,215 women between ages of 16-26. Participants were randomized to the 9vHPV vaccine group or the qHPV vaccine group and each received a series of three IM injections (day 1, 2, and 6 mo). Swabs of labial, vulvar, perineal, perianal, endocervical, and ectocervical tissue was obtained and used for HPV DNA testing/Pap smear.
**Results**: Rate of high-grade cervical, vulvar, or vaginal disease was 14.0 per 1000 person-years in both vaccine groups. The rate of high-grade cervical, vulvar, or vaginal disease related to HPV-31, 33, 45, 52, and 58 was 0.1 per 1000 person-years in the 9vHPV group and 1.6 per 1000 person-years in the qHPV group (95% CI = 80.9-99.8). Antibody responses to HPV-6, 11, 16, and 18 were not significantly different between the two vaccine groups although adverse events related to injection sites were more common in the 9vHPV group.
**Conclusions**: The 9vHPV vaccine was non-inferior to qHPV vaccine in preventing infection and disease related to HPV-6, 11, 16, and 18 and also covered additional oncogenic types HPV-31, 33, 45, 52, and 58 in a susceptible population.

### Treatment
- first episode: acyclovir 200 mg PO five times daily x 7-10 d, or famciclovir 250 mg PO tid x 7-10 d or valacyclovir 1 g PO bid x 7-10 d
- recurrent episode: acyclovir 400 mg PO tid x 5 d, valacylovir 1 g PO OD x 5 d or famciclovir 250 mg PO BID x 5 d
- daily suppressive therapy
  - consider for >6 recurrences per yr or recurrence every 2 mo
  - acyclovir 400 mg PO bid or valacyclovir 500 mg PO OD or valacyclovir 1 g PO OD or famciclovir 250 mg PO bid
- severe disease: IV acyclovir 5-10 mg/kg IV q8h x 2-7 d or until clinical improvement observed followed by oral antiviral therapy to complete 10 d of therapy total
- education regarding transmission: avoid sexual contact from onset of prodrome until lesions have cleared, use barrier contraception

## SYPHILIS

### Etiology
- Treponema pallidum



**Epidemiology of Genital Ulcers**

| | |
|---|---|
| HSV | 70-80% |
| 1° Syphilis | 5% |
| Chancroid (*Haemophilus ducreyi*) | <1% |

### Classifications
- primary syphilis
  - 3-4 wk after exposure
  - painless chancre on vulva, vagina, or cervix
  - painless inguinal lymphadenopathy
  - serological tests usually negative, local infection only
- secondary syphilis (can resolve spontaneously)
  - 2-6 mo after initial infection
  - nonspecific symptoms: malaise, anorexia, headache, diffuse lymphadenopathy
  - generalized maculopapular rash: palms, soles, trunk, limbs
  - condylomata lata: anogenital, broad-based, fleshy, grey lesions
  - serological tests usually positive
- latent syphilis
  - no clinical manifestations; detected by serology only
- tertiary syphilis
  - may involve any organ system
  - neurological: tabes dorsalis, general paresis
  - cardiovascular: aortic aneurysm, dilated aortic root
  - vulvar gumma: nodules that enlarge, ulcerate, and become necrotic (rare)
- congenital syphilis
  - may cause fetal anomalies, stillbirths, or neonatal death

### Investigations
- aspiration of ulcer serum or node
- darkfield microscopy (most sensitive and specific diagnostic test for syphilis): look for spirochetes
- non-treponemal screening tests (VDRL, RPR); non-reactive after treatment, can be positive with other conditions
- specific anti-treponemal antibody tests (FTA-ABS, MHA-TP, TP-PA)
  - confirmatory tests; remain reactive for life (even after adequate treatment)

### Treatment
- reportable disease, partners should be referred for treatment
- treatment of primary, secondary, latent syphilis of <1 yr duration
  - benzathine penicillin G 2.4 million units IM single dose
- treatment of latent syphilis of >1 yr duration
  - benzathine penicillin G 2.4 million units IM q1wk x 3 wk
- treatment of neurosyphilis
  - IV aqueous penicillin G 3-4 million units IM q4h x 10-14 d
- screening
  - high-risk groups
  - in pregnancy (see Obstetrics, *Infections During Pregnancy*, OB29)

### Complications
- if untreated, 1/3 will experience late complications

### HIV
- see Infectious Diseases, ID25

# Bartholin Gland Abscess

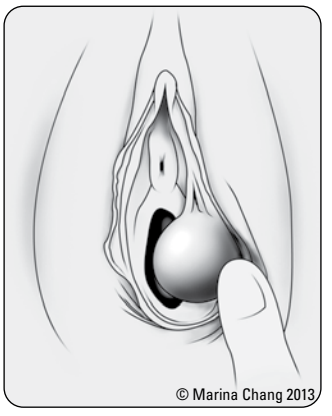


**Figure 14. Bartholin gland abscess**

### Etiology
- often anaerobic and polymicrobial
- *U. urealyticum, N. gonorrhoeae, C. trachomatis, E. coli, P. mirabilis, Streptococcus* spp., *S. aureus* (rare)
- blockage of duct

### Clinical Features
- unilateral swelling and pain in inferior lateral opening of vagina
- sitting and walking may become difficult and/or painful

### Treatment
- sitz baths, warm compresses
- antibiotics: cephalexin x 1 wk
- incision and drainage using local anesthesia with placement of Word catheter (10 French latex catheter) for 2-3 wk (or as long as stays in situ)
- marsupialization under general anesthetic: more definitive treatment
- rarely treated by removing gland

# Pelvic Inflammatory Disease

PID accounts for up to 20% of all gynecological hospital admissions

- up to 20% of all gynecology-related hospital admissions
- inflammation of the upper genital tract (above the cervix) including endometrium, fallopian tubes, ovaries, pelvic peritoneum ± contiguous structures

### Etiology
- causative organisms (in order of frequency)
  - *C. trachomatis*
  - *N. gonorrhoeae*
    - gonorrhea and chlamydia often co-exist
  - endogenous flora: anaerobic, aerobic, or both
    - *E. coli, Staphylococcus, Streptococcus, Enterococcus, Bacteroides, Peptostreptococcus, H. influenzae, G. vaginalis*
    - cause of recurrent PID
    - associated with instrumentation
  - *Actinomyces israelii* (Gram-positive, non-acid-fast anaerobe)
    - 1-4% of PID cases associated with IUDs
  - others (TB, Gram-negatives, CMV, *U. urealyticum*, etc.)

### Risk Factors
- age <30 yr
- risk factors as for chlamydia and gonorrhea
- vaginal douching
- IUD (within first 10 d after insertion)
- invasive gynecologic procedures (D&C, endometrial biopsy)

### Clinical Feature
- up to 2/3 asymptomatic: many subtle or mild symptoms
- common: fever >38.3°C, lower abdominal pain and tenderness, abnormal discharge (cervical or vaginal)
- uncommon: N/V, dysuria, AUB
- chronic disease (often due to chlamydia)
  - constant pelvic pain
  - dyspareunia
  - palpable mass
  - very difficult to treat, may require surgery

**PID Diagnosis**
**Must have**
- Lower abdominal pain

**Plus one of**
- Cervical motion tenderness
- Adnexal tenderness

**Plus one or more of**
- High risk partner
- Temperature >38°C
- Mucopurulent cervical discharge
- Positive culture for *N. gonorrhoeae, C. trachomatis, E. coli,* or other vaginal flora
- Cul-de-sac fluid, pelvic abscess or inflammatory mass on U/S or bimanual
- Leukocytosis
- Elevated ESR or CRP (not commonly used)

### Investigations
- blood work
  - β-hCG (must rule out ectopic pregnancy), CBC, blood cultures if suspect septicemia
- urine R&M
- speculum exam, bimanual exam
  - vaginal swab for Gram stain, C&S
  - cervical cultures for *N. gonorrhoeae, C. trachomatis*
  - endometrial biopsy will give definitive diagnosis (rarely done)
- ultrasound
  - may be normal
  - free fluid in cul-de-sac
  - pelvic or tubo-ovarian abscess
  - hydrosalpinx (dilated fallopian tube)
- laparoscopy (gold standard)
  - for definitive diagnosis: may miss subtle inflammation of tubes or endometritis

## Treatment

- must treat with polymicrobial coverage

**Table 16. Inpatient and Outpatient Management Options for Pelvic Inflammatory Disease**

| | Inpatient | Outpatient |
|---|---|---|
| **Indications** | Moderate to severe illness<br>Atypical infection<br>Adnexal mass, tubo-ovarian mass, or pelvic abscess<br>Unable to tolerate oral antibiotics or failed oral therapy<br>Immunocompromised<br>Pregnant<br>Adolescent (first episode)<br>Surgical emergency cannot be excluded (e.g. ovarian torsion)<br>PID is secondary to instrumentation | Typical findings<br>Mild to moderate illness<br>Oral antibiotics tolerated<br>Compliance ensured<br>Follow-up within 48-72 h (to ensure symptoms not worsening) |
| **Antibiotic Regimen** | Cefoxitin 2 g IV q6h + doxycycline 100 mg PO/IV q12h or<br>Clindamycin 900 mg IV q8h + gentamycin 2 mg/kg IV/IM loading dose then gentamycin 1.5 mg/kg q8h maintenance dose<br>Continue IV antibiotics for 24 h after symptoms have improved then doxycycline 100 mg PO bid to complete 14 d<br>Percutaneous drainage of abscess under U/S guidance<br>When no response to treatment, laparoscopic drainage<br>If failure, treatment is surgical (salpingectomy, TAH/BSO) | 1st line: ceftriaxone 250 mg IM x 1 + doxycycline 100 mg PO bid x 14 d or cefoxitin 2 g IM x 1 + probenecid 1 g PO + doxycycline 100 mg PO bid ± metronidazole 500 mg PO bid x 14 d<br>2nd line: ofloxacin 400 mg PO bid x14 d or levofloxacin 500 mg PO OD x 14 d ± metronidazole 500 mg PO bid x 14 d<br>Consider removing IUD after a minimum of 24 h of treatment<br>Reportable disease<br>Treat partners<br>Consider re-testing for *C. trachomatis* and *N. gonorrhoeae* 4-6 wk after treatment if documented infection |

## Complications of Untreated PID

- chronic pelvic pain
- abscess, peritonitis
- adhesion formation
- ectopic pregnancy
- infertility
  - 1 episode of PID: 13% infertility
  - 2 episodes of PID: 36% infertility
- bacteremia
- septic arthritis, endocarditis

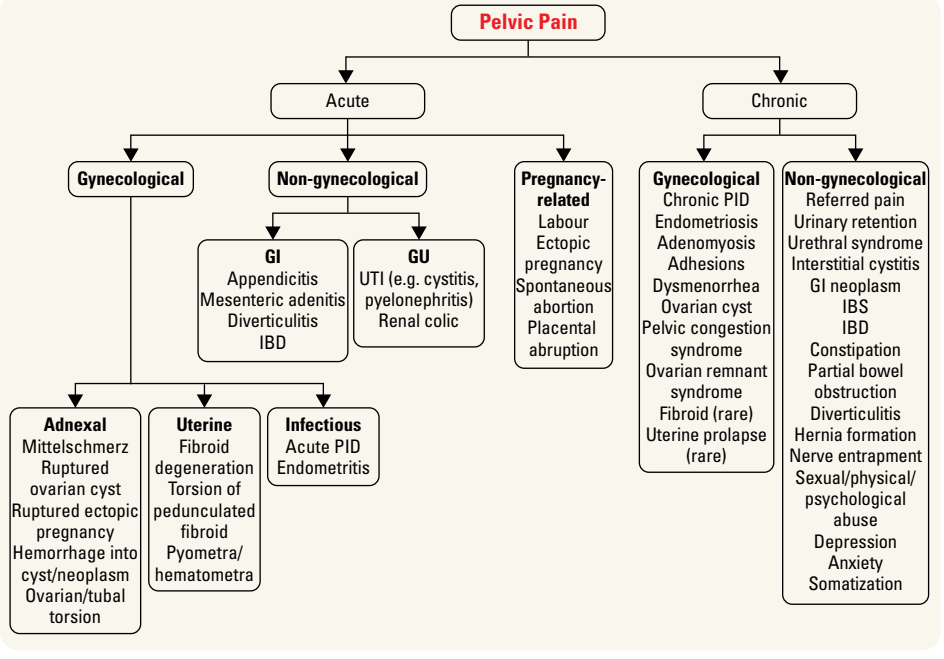



**Figure 15. Approach to pelvic pain**

# Toxic Shock Syndrome

- see Infectious Diseases, ID21

### Risk Factors
- tampon use
- diaphragm, cervical cap, or sponge use (prolonged use, i.e. >24 h)
- wound infections
- post-partum infections
- early recognition and treatment of syndrome is imperative as incorrect diagnosis can be fatal



**Toxic Shock Syndrome**
Multiple organ system failure due to *S. aureus* exotoxin (rare condition)

### Clinical Feature
- sudden high fever
- sore throat, headache, diarrhea
- erythroderma
- signs of multisystem organ failure
- refractory hypotension
- exfoliation of palmar and plantar surfaces of the hands and feet 1-2 wk after onset of illness

### Treatment
- remove potential sources of infection (foreign objects and wound debris)
- debride necrotic tissues
- adequate hydration
- penicillinase-resistant antibiotics (e.g. cloxacillin)
- steroid use controversial, but, if started within 72 h, may reduce severity of symptoms and duration of fever

# Surgical Infections

### Post-Operative Infections in Gynecological Surgery
- pelvic cellulitis
  - common post hysterectomy, affects vaginal vault
  - erythema, induration, tenderness, discharge involving vaginal cuff
  - treat if fever and leukocytosis with broad-spectrum antibiotics (i.e. clindamycin and gentamicin)
  - drain if excessive purulence or large mass
  - can result in intra-abdominal and pelvic abscess
- see General Surgery, *Post-Operative Fever*, GS7

# Sexual Abuse

- see Family Medicine, FM26, Emergency Medicine, ER27

# Sexuality and Sexual Dysfunction

### SEXUAL RESPONSE
1. desire: energy that allows an individual to initiate or respond to sexual stimulation
2. arousal: physical and emotional stimulation leading to breast and genital vasodilation and clitoral engorgement
3. orgasm: physical and emotional stimulation is maximized, allowing the individual to relinquish their sense of control
4. resolution: most of the congestion and tension resolves within seconds, complete resolution may take up to 60 min

### SEXUAL DYSFUNCTION

### Etiology
- psychological or emotional: depression, abuse
- hormonal: menopause
- neurologic dysfunction: spinal cord injury
- vascular insufficiency: DM
- drug side effects: β-blockers
- trauma: episiotomy

### Classification
- lack of desire (60-70% of women)
- lack of arousal
- anorgasmia (5-10%)
  - primary anorgasmia: never before achieved orgasm under any circumstances
  - secondary anorgasmia: was able to achieve orgasms before but now unable to

- dyspareunia (3-6%): painful intercourse, superficial or deep
  - vaginismus (15%)
  - vulvodynia
  - vaginal atrophy
  - vulvar vestibulitis: associated with history of frequent yeast infections
  - PID

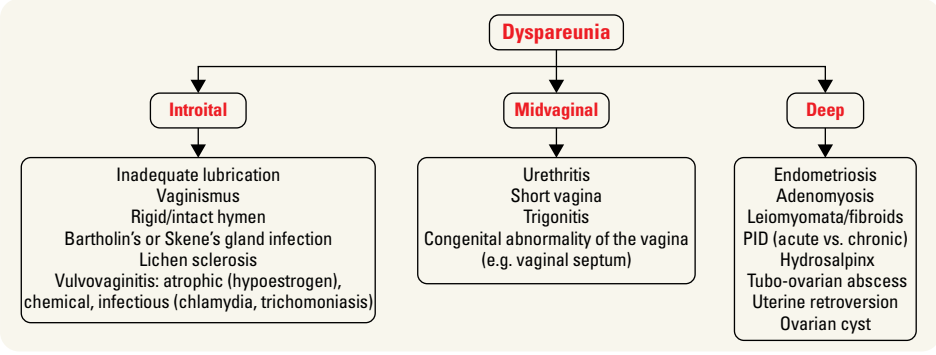



**Figure 16. Approach to dyspareunia**

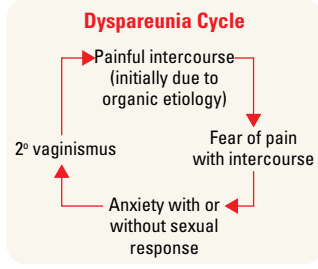



**Figure 17. Dyspareunia cycle**

### Treatment
- lack of desire: assess factors, rule out organic causes, relationship therapy, sensate focus exercises
- anorgasmia: self-exploration/pleasuring, relationship therapy if needed, bridging techniques (different sexual positions, clitoral stimulation during intercourse)
- dyspareunia
  - Kegel and reverse Kegel exercises
  - dilator treatment
  - comfort with self-exam
  - psychotherapy, other behavioural techniques
  - female on top position: allows for control of speed and duration
  - vestibulitis: remove local irritants, change in contraceptive methods, dietary changes (increased citrate, decreased oxalate), and vestibulectomy (rare)
  - vulvodynia: local moisturization, cold compresses, systemic nerve-blocking therapy (amitriptyline, gabapentin) orally or topically, topical anesthetics, estrogen cream
  - pain clinic
  - removal of environmental factors: bubble baths, soaps, perfumes, sanitary pads with plastic lining

**Kegel Exercises**
Regular contraction and relaxation to strengthen pelvic floor muscles

**Reverse Kegel Exercises**
1 s contraction then 5 s of relaxation

# Menopause

- see Family Medicine, FM40

### Definitions
- lack of menses for 1 yr
- types of menopause
  - physiological; average age 51 yr (follicular atresia)
  - primary ovarian insufficiency; before age 40 (autoimmune disorder, infection, Turner's syndrome)
  - iatrogenic (surgical/radiation/chemotherapy)

**Menopause**
Occurrence of last spontaneous menstrual period, resulting from loss of ovarian function (loss of oocyte response to gonadotropins)

**"Being in menopause"**
Lack of menses for 1 yr

**Perimenopause**
Period of time surrounding menopause (2-8 yr preceding + 1 yr after last menses) characterized by fluctuating hormone levels, irregular menstrual cycles, and symptom onset

### Clinical Features
- associated with estrogen deficiency
  - vasomotor instability (tends to dissipate with time)
    - hot flushes/flashes, night sweats, sleep disturbances, formication, nausea, palpitations
  - urogenital atrophy involving vagina, urethra, bladder
    - dyspareunia, pruritus, vaginal dryness, bleeding, post-coital bleeding, urinary frequency, urgency, incontinence
    - inspection may reveal: thinning of tissues, erythema, petechiae, bleeding points, dryness on speculum exam
  - skeletal
    - osteoporosis, joint and muscle pain, back pain
  - skin and soft tissue
    - decreased breast size, skin thinning/loss of elasticity
  - psychological
    - increased anxiety, depression, irritability, fatigue, decreased libido, memory loss

- 85% of women experience hot flashes
- 20-30% seek medical attention
- 10% are unable to work

### Investigations
- increased levels of FSH (>35 IU/L) on day 3 of cycle (if still cycling) and LH (FSH>LH)
- FSH level not always predictive due to monthly variation; use absence of menses for 1 yr to diagnose
- decreased levels of estradiol (later)

## Treatment

### Table 17. Treatment of Menopause

| Goal is for individual symptom management | | | | | | |
|---|---|---|---|---|---|---|
| **Vasomotor Instability** | **Vaginal Atrophy** | **Urogenital Health** | **Osteoporosis** | **Decreased Libido** | **CVD*** | **Mood And Memory** |
| HRT (first line)<br>SSRI<br>venlafaxine<br>gabapentin<br>propranaolol<br>clonidine<br>acupuncture | Local estrogen: cream (Premarin®), vaginal suppository (VagiFem®), ring (Estring®), lubricants (Replens®), oral or transdermal hormone replacement therapy, intravaginal laser | Lifestyle changes (weight loss, bladder re-training), local estrogen replacement, surgery | 1000-1500 mg calcium OD, 800-1000 IU vitamin D, weight-bearing exercise, smoking cessation, bisphosphonates (e.g. alendronate), selective estrogen receptor modifiers (SERMs) (e.g.raloxifene [Evista®]), HRT (second-line treatment) | Vaginal lubrications, counselling, androgen-replacement testoterone cream or the oral form (Andriol®) | Manage CVD risk factors | Anti-depressants (first line), HRT (augments effect) |

*CVD (cardiovascular disease)

**Menopause Pathophysiology**

Degenerating theca cells fail to react to endogenous gonadotropins (FSH, LH)
↓
Less estrogen is produced
↓
Decreased negative feedback on hypothalamic-pituitary-adrenal axis
↓
Increased FSH and LH
↓
Stromal cells continue to produce androgens as a result of increased LH stimulation

**Figure 18. Menopause pathophysiology**

- Osteoporosis is the single most important health hazard associated with menopause
- Cardiovascular disease is the leading cause of death post-menopause

- Increased risk of breast cancer (RR 1.3) is associated with estrogen+progesterone HRT, but not with estrogen-only HRT
- All women taking HRT should have periodic surveillance and counselling regarding its benefits and risks

# Hormone Replacement Therapy

- see Family Medicine, FM40
- primary indication is treatment of menopausal symptoms (vasomotor instability)
- keep doses low (e.g. 0.3 mg Premarin®) and duration of treatment short (<5 yr)

## HRT Components

- estrogen
- oral or transdermal (e.g. patch, gel)
- transdermal preferred for women overall, especially with hypertriglyceridemia or impaired hepatic function, smokers, and women who suffer from headaches associated with oral HRT
- low-dose (preferred dose: 0.3 mg Premarin®/25 µg Estradot® patch, can increase if necessary)
- progestin
- given in combination with estrogen for women with an intact uterus to prevent development of endometrial hyperplasia/cancer

### Table 18. Examples of HRT Regimens

| HRT Regimen | Estrogen Dose | Progestin Dose | Notes |
|---|---|---|---|
| **Unopposed Estrogen** | CEE 0.625 mg PO OD | None | If no intact uterus |
| **Standard-Dose** | CEE 0.625 mg PO OD | MPA 2.5 mg PO OD, or micronized progesterone 100 mg PO OD | Withdrawal bleeding may occur in a spotty, unpredictable manner<br>Usually abates after 6-8 mo due to endometrial atrophy<br>Once patient has become amenorrheic on HRT, significant subsequent bleeding episodes require evaluation (endometrial biopsy) |
| **Standard-Dose Cyclic** | CEE 0.625 mg PO OD | MPA 5-10 mg PO days 1-14 only, or micronized progesterone 200 mg PO OD days 1-14 only | Bleeding occurs monthly after day 14 of progestin (can continue for years)<br>PMS-like symptoms (breast tenderness, fluid retention, headache, nausea) are more prominent with cyclic HRT |
| **Pulsatile** | CEE 0.625 mg PO OD | MPA low-dose | 3 d on, 3 d off |
| **Transdermal** | Estroderm®-Estradiol 0.05 mg/d or 0.1 mg/d<br>Estalis®-Estradiol 140 µg/d or 250 µg/d | Estroderm®-MPA 2.5 mg PO OD<br>Estalis®-NEA 50 µg/d | Use patch twice weekly<br>Can use oral progestins (Estroderm®)<br>Combined patches available (Estalis®) |
| **Topical** | Estrace® 2-4 g/d x 1-2 wk, 1 g/d maintenance<br>Premarin® 0.5-2 g/d for 21 d then off 7 d for vaginal atrophy, 0.5 g/d for 21 d then off 7 d or twice/wk for dyspareunia<br>Estragyn® 2-4 g/d | Crinone® 4% or 8% (45 or 90 mg applicator) | If simultaneously taking oral estrogen tablet, may need to adjust dosing<br>If intact uterus, also take progesterone |

CEE = conjugated equine estrogen (e.g. Premarin®); MPA = medroxyprogesterone acetate (e.g. Provera®); NEA = norethindrone acetate
Consider lower dose regimens, PREMPRO® 0.45/1.5 (Premarin® 0.45 mg and Provera® 1.5 mg); Estrace® (topical 17β-estradiol) = 0.1 mg active ingredient/g; Premarin® (topical CEE) = 0.625 mg active ingredient/g; Estragyn® (topical estrone) = 1 mg active ingredient/g

## Side Effects of HRT

- abnormal uterine bleeding
- mastodynia: breast tenderness and swelling
- edema, bloating, heartburn, nausea
- mood changes (progesterone)
- can be worse in progesterone phase of combined therapy

## Contraindications to HRT

- absolute
  - acute liver disease
  - undiagnosed vaginal bleeding
  - history of breast cancer
  - known or suspected uterine cancer/breast cancer
  - acute vascular thrombosis or history of severe thrombophlebitis or thromboembolic disease
  - cardiovascular disease
- relative
  - pre-existing uncontrolled HTN
  - uterine fibroids and endometriosis
  - familial hyperlipidemias
  - migraine headaches
  - family history of estrogen-dependent cancer
  - chronic thrombophlebitis
  - DM (with vascular disease)
  - gallbladder disease, hypertriglyceridemia, impaired liver function (consider transdermal estrogen)
  - fibrocystic disease of the breasts

**Absolute Contraindications to HRT**

**ABCD**
**A**cute liver disease
Undiagnosed vaginal **B**leeding
**C**ancer (breast/uterine), **C**ardiovascular disease
**D**VT (thromboembolic disease)

## WOMEN'S HEALTH INITIATIVE (launched in 1991)

- two non-randomized studies investigating health risks and benefits of HRT in healthy postmenopausal women 50-79 yr old
  - continuous combined HRT (CEE 0.625 mg + MPA 2.5 mg OD) in 16,608 women with an intact uterus
  - estrogen-alone (CEE 0.625 mg) in 10,739 women with a previous hysterectomy
- both arms of the trial were stopped early because of evidence of increased risk of breast cancer, stroke, PE, and CHD in the combined HRT arm, and increased risk of stroke with no CHD benefits in the estrogen-alone arm
- the apparent increase in CHD was in disagreement with results of previous observational trial
- results of the WHI study have since been challenged and revision of how CHD was diagnosed led to loss of statistical significance of the results
- benefits and risks reported as number of cases per 10,000 women each year

**Table 19. HRT Benefits vs. Risks**

| Benefits | Risks |
|---|---|
| **Vasomotor Symptoms**: less frequent and severe with use of either combined or estrogen alone HRT | **Stroke**: 8 additional cases with combined HRT and 12 additional cases for estrogen alone (WHI) |
| **Osteoporosis**: 5 fewer cases of hip fractures and 47 fewer cases of all fractures with combined HRT; 6 fewer cases of hip fractures with estrogen alone | **DVT/PE**: 18 additional cases with combined HRT and 9 additional cases for estrogen-alone (WHI) |
| **Colon Cancer**: 6 fewer cases with combined HRT (WHI); one additional case with estrogen alone | **CHD**: 7 additional MIs with combined HRT (WHI); secondary analysis suggests greater absolute risk for women aged >70 yr and for women who start HRT >10 yr post-menopause |
| | **Breast Cancer**: 8 additional cases with combined HRT (WHI); risk only increased after >5 yr of combined HRT use; no increased risk for estrogen alone |
| | **Dementia and Mild Cognitive Impairment**: 50% greater risk of developing dementia in women taking estrogen alone after age 65; risk is greater for women taking combined HRT; risk of developing dementia was reduced for women taking HRT before age 65 |

**Long-Term Hormone Therapy for Perimenopausal and Postmenopausal Women**
Cochrane DB Syst Rev 2012;7:CD004143
**Purpose**: To determine the effect of long-term HRT on mortality, cardiovascular outcomes, cancer, gallbladder disease, fractures, cognition, and QOL in perimenopausal and postmenopausal women, during HRT use, and after cessation of HRT.
**Results**: 23 studies with 42,380 women included. 70% of the data from the WHI (1998) and HERS (1998). None of the studies focused on perimenopausal women. Combined continuous HRT: increased risk of coronary event after 1 yr (absolute risk 18/1000, 95% CI 3-7), venous thromboembolism after 1 yr (AR 7/1000, 95% CI 4-11), stroke after 3 yr (AR 18/1000, 95% CI 14-23), breast cancer after 5.6 yr (AR 23/1000, 95% CI 19-29), gallbladder disease after 5.6 yr (AR 27/1000, 95% CI 21-34), and death from lung cancer after 5.6 yr use (AR 9/1000, 95% CI 6-13). Estrogen only HRT: increased risk of venous thromboembolism after 1-2 yr use (AR 5/1000, 95% CI 2-10; after 7 yr AR 21/1000, 95% CI 16-28), stroke after 7 yr (AR 32/1000, 95% CI 25-40), and gallbladder disease after 7 yr use (AR 45/1000, 95% CI 36-57) and did not significantly affect the risk of breast cancer. Women >65 yr of age taking combined HRT had a statistically significant increase in the incidence of dementia after 4 yr use (AR 18/1000, 95% CI 11-30). Women taking HRT had a decreased risk of fractures with combined HRT after 5.6 yr (AR 86/1000, 95% CI 79-84) and 7.1 yr of estrogen only HRT (AR 102/1000, 95% CI 91-112).
**Conclusions**: HRT is not indicated for primary or secondary prevention of cardiovascular disease or dementia. Although HRT is considered effective for the prevention of postmenopausal osteoporosis, it is generally recommended as an option only for women at significant risk, for whom non-estrogen therapies are unsuitable.

# Urogynecology

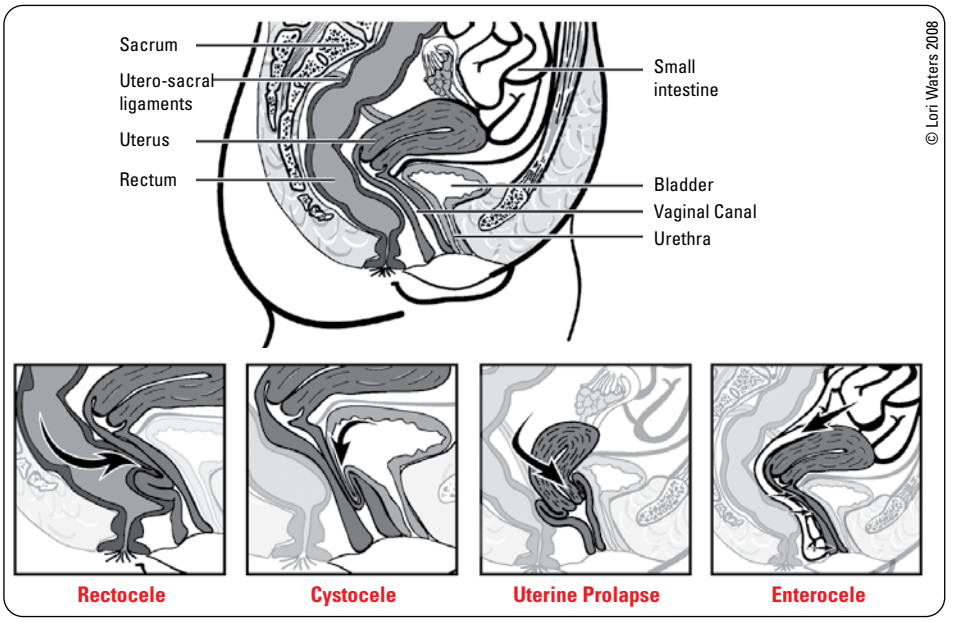



**Figure 19. Pelvic anatomy**

## Prolapse

### Etiology

- relaxation, weakness, or defect in the cardinal and uterosacral ligaments which normally maintain the uterus in an anteflexed position and prevent it from descending through the urogenital diaphragm (i.e. levator ani muscles)
- related to:
  - vaginal childbirth
  - aging
  - decreased estrogen (post-menopause)
  - following pelvic surgery
  - increased intra-abdominal pressure (obesity, chronic cough, constipation, ascites, heavy lifting)
  - congenital (rarely)
  - ethnicity (Caucasian women > Asian or African women)
  - collagen disorders

### GENERAL CONSERVATIVE TREATMENT

(for pelvic relaxation/prolapse and urinary incontinence)

- Kegel exercises
- local vaginal estrogen therapy
- vaginal pessary (intravaginal suspension disc)

**Grading of Pelvic Organ Prolapse**

- 0 = no descent during straining
- 1 = distal portion of prolapse >1 cm above level of hymen
- 2 = distal portion of prolapse ≤1 cm above or below level of hymen
- 3 = distal portion of prolapse >1 cm below level of hymen but without complete vaginal eversion
- 4 = complete eversion of total length of lower genital tract
- Procidentia: failure of genital supports and complete protrusion of uterus through the vagina

**Pelvic Relaxation/Prolapse**

Protrusion of pelvic organs into or out of the vagina

**Table 20. Pelvic Prolapse**

| Type | Clinical Features | Treatment |
|---|---|---|
| **Cystocele** (protrusion of bladder into the anterior vaginal wall) | Frequency, urgency, nocturia<br>Stress incontinence<br>Incomplete bladder emptying ± associated increased incidence of UTIs (may lead to renal impairment) | See above<br>Anterior colporrhaphy ("anterior repair")<br>Consider additional/alternative surgical procedure if documented urinary stress incontinence |
| **Enterocele** (prolapse of small bowel in upper posterior vaginal wall) | | Similar to hernia repair<br>Contents reduced, neck of peritoneal sac ligated, uterosacral ligaments, and levator ani muscles approximated |
| **Rectocele** (protrusion of rectum into posterior vaginal wall) | Straining/digitation to evacuate stool<br>Constipation | See above<br>Also laxatives and stool softeners<br>Posterior colporrhaphy ("posterior repair"), plication of endopelvic fascia and perineal muscles approximated in midline to support rectum and perineum (can result in dyspareunia) |
| **Uterine Prolapse** (protrusion of cervix and uterus into vagina) | Groin/back pain (stretching of uterosacral ligaments)<br>Feeling of heaviness/pressure in the pelvis<br>Worse with standing, lifting<br>Worse at the end of the day<br>Relieved by lying down<br>Ulceration/bleeding (particularly if hypoestrogenic)<br>± urinary incontinence | See above<br>Vaginal hysterectomy ± surgical prevention of vault prolapse<br>Consider additional surgical procedures if urinary incontinence, cystocele, rectocele, and/or enterocele are present |
| **Vault Prolapse** (protrusion of apex of vaginal vault into vagina, post-hysterectomy) | | See above<br>Sacralcolpopexy (vaginal vault suspension), sacrospinous fixation, or uterosacral ligament suspension |



The only **true** hernia of the pelvis is an ENTEROCELE because peritoneum herniates with the small bowel

# Urinary Incontinence

• see Urology, U6

## STRESS INCONTINENCE

### Definition
• involuntary loss of urine with increased intra-abdominal pressure (cough, laugh, sneeze, walk, run)

## RISK FACTORS FOR STRESS INCONTINENCE IN WOMEN
• age
• obesity
• parity
• vaginal delivery
• pelvic prolapse
• pelvic surgery
• hypoestrogenic state (post-menopause)
• smoking
• neurological/pulmonary disease

### Treatment
• see *Prolapse*, GY36
• surgical
  ▪ tension-free vaginal tape (TVT), tension-free obturator tape (TOT), prosthetic/fascial slings or retropubic bladder suspension (Burch or Marshall-Marchetti-Krantz procedures)

## URGE INCONTINENCE

### Definition
• urine loss associated with an abrupt, sudden urge to void
• "overactive bladder"
• diagnosed based on symptoms



**Urge Incontinence**
Urine loss associated with an abrupt, sudden urge to void

### Etiology
• idiopathic (90%)
• detrusor muscle overactivity ("detrusor instability")

### Associated Symptoms
• frequency, urgency, nocturia, leakage



**Rule Out Neurological Causes of Urge Incontinence**
• MS
• Herniated disc
• DM

### Treatment
• behaviour modification (reduce caffeine/liquid, smoking cessation, regular voiding schedule)
• Kegel exercises
• medications
  ▪ anticholinergics: oxybutinin (Ditropan®), tolterodine (Detrol®), solifenacin (VESIcare®)
  ▪ tricyclic antidepressants: imipramine

# Gynecological Oncology

## Pelvic Mass

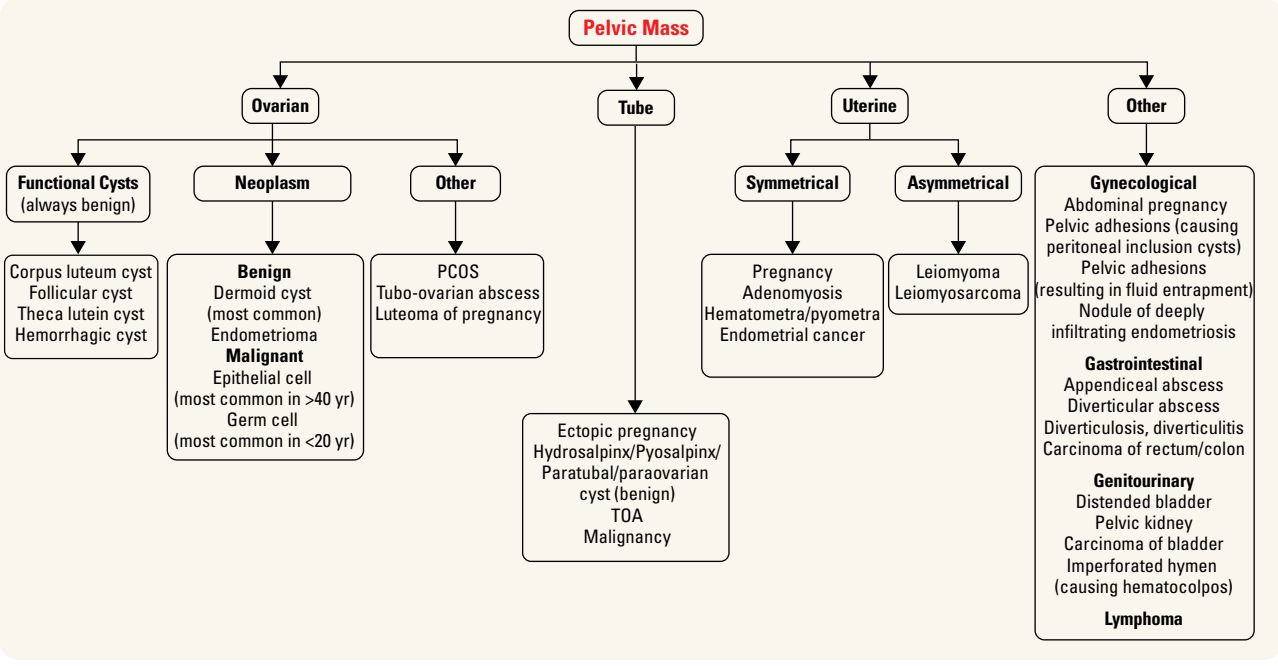



**Figure 20. Differential diagnosis of pelvic mass**

## Uterus

### ENDOMETRIAL CARCINOMA

#### Epidemiology

- most common gynecological malignancy in North America (40%); 4th most common cancer in women
- 2-3% of women develop endometrial carcinoma during lifetime
- mean age is 60 yr
- majority are diagnosed in early stage due to detection of symptoms
- 85-90% 5 yr survival for stage I disease
- 70-80% 5 yr survival for all stages

**Table 21. Features of Type I and Type II Endometrial Cancer**

| | Type I | Type II |
|---|---|---|
| **Description** (Both types related to estrogen, but Type II to a lesser degree) | Characterized as estrogen-related (i.e. excess/unopposed estrogen):<br>Endometrioid<br>Includes well-differentiated endometrioid adenocarcinoma | Characterized as non-estrogen related:<br>Non-endometrioid<br>Includes serous, clear cell, grade 4 endometrioid and undifferentiated carcinomas, as well as carcinosarcoma<br>More aggressive histologic subtypes; prognosis typically worse than type I, with a poorer 5 yr survival |
| **Risk Factors** (Increasing age and family history are risk factors for both types) | PCOS<br>Diabetes mellitus<br>Unbalanced HRT (balanced HRT is protective)<br>Nulliparity<br>Late menopause (>55 yr), early menarche<br>Estrogen-producing ovarian tumours (e.g. granulosa cell tumours)<br>HNPCC (hereditary non-polyposis colorectal cancer)/Lynch II syndrome<br>Tamoxifen | Parous women<br>Increasing age of menarche and number of children not significantly associated with reduced risk in clear-cell endometrial carcinoma<br>Has been associated with p53 mutations |
| **Clinical Features** | ~80% of cases<br>Postmenopausal bleeding in majority<br>Abnormal uterine bleeding in majority of affected pre-menopausal women (menorrhagia, intermenstrual bleeding) | ~15% of cases<br>Post-menstrual bleeding<br>Abnormal uterine bleeding |

**Incidence of Malignant Gynecological Lesions in North America**
endometrium > ovary > cervix > vulva > vagina > fallopian tube

**Risk Factors for Endometrial Cancer**

**COLD NUT**
**C**ancer (ovarian, breast, colon)
**O**besity
**L**ate menopause
**D**iabetes mellitus
**N**ulliparity
**U**nopposed estrogen: PCOS, anovulation, HRT
**T**amoxifen: chronic use

Postmenopausal bleeding = endometrial cancer until proven otherwise (95% present with vaginal bleeding)

An endometrial thickness of 5 mm or more is considered abnormal in a postmenopausal woman with vaginal bleeding

## Screening
- no known benefit for mass screening
- annual endometrial sampling starting at age 30-35 only for women at high risk (HNPCC [Hereditary Non-Polyposis Colorectal Cancer]/ Lynch II syndrome)
- routine pelvic ultrasound should not be used as screening test (high false positives)

## Investigations
- endometrial sampling
  - office endometrial biopsy
  - D&C ± hysteroscopy
- ± pelvic ultrasound (in women where adequate endometrial sampling not feasible without invasive methods)
  - not acceptable as alternative to pelvic exam or endometrial sampling to rule out cancer

**Table 22. FIGO Staging of Endometrial Cancer (2009)**

| Stage | Description | Stage | Description |
|---|---|---|---|
| **I** | Confined to corpus uteri including endocervical glandular involvement | **IIIC** | Metastasis to pelvic ± para-aortic LNs |
| **IA** | No or less than half myometrial invasion | **IIIC1** | Positive pelvic LN |
| **IB** | Invades through ≥½ of myometrium | **IIIC2** | Positive para-aortic LN ± positive pelvic LNs |
| II | Tumour invades cervical stroma, but does not extend beyond uterus* | IV | Invasion of bladder ± bowel mucosa ± distant metastases (note: omental disease is stage IV) |
| III | Tumour involving serosa, adnexa, vagina, or parametrium | **IVA** | Invasion of bladder ± bowel mucosa |
| **IIIA** | Invasion of serosa ± adnexae | **IVB** | Distant mets, including intra-abdominal and intraperitoneal mets ± inguinal LNs |
| **IIIB** | Vaginal ± parametrial involvement | | |

FIGO: International Federation of Gynecology and Obstetrics *Note: endocervical glandular involvement is now considered as Stage I (previously Stage II)

## Treatment
- surgical: hysterectomy/bilateral salpingo-oophorectomy (BSO) and pelvic washings ± pelvic and para-aortic node dissection ± omentectomy
  - goals: diagnosis, staging, treatment, defining optimal adjuvant treatment
  - laparoscopic approach associated with improved quality of life (optimal for most patients)
- adjuvant radiotherapy (for improved local control in patients at risk for local recurrence) and adjuvant chemotherapy (in patients at risk for distant recurrence or with metastatic disease): based on presence of poor prognostic factors in definitive pathology
- chemotherapy: often used for recurrent disease (if high grade or aggressive histology)
- hormonal therapy: progestins can be used for recurrent disease (especially if low-grade)

**Prognostic Factors**
Most important is FIGO stage
Other Prognostic Factors:
- Age
- Grade
- Histologic subtype
- Depth of myometrial invasion
- Presence of lymphovascular space involvement (LVSI)

**Complications of Therapy**

**Surgical Complications**
- Surgical site infection
- Lymphedema

**Radiation Complications**
- Radiation fibrosis
- Cystitis
- Proctois

**Uterine Sarcoma – Symptoms**
**BAD-P**
**B**leeding
**A**bdominal distention
Foul-smelling vaginal **D**ischarge
**P**elvic pressure

A rapidly enlarging uterus, especially in a postmenopausal woman, should prompt consideration of leiomyosarcoma. Nevertheless, all postmenopausal patients with an enlarging uterus should have an endometrial biopsy

## UTERINE SARCOMA
- rare; 3-9% of all uterine malignancies
- arise from stromal components (endometrial stroma, mesenchymal or myometrial tissues)
- behave more aggressively and are associated with worse prognosis than endometrial carcinoma; 5 yr survival is 35%
- vaginal bleeding is most common presenting symptom

**Table 23. Summary of Uterine Sarcoma Subtypes and Features**

| Type | Epidemiology | Features | Diagnosis | Treatment |
|---|---|---|---|---|
| **PURE TYPE** | | | | |
| **1. Leiomyosarcoma** | Most common type of uterine sarcoma<br>Average age of presentation is 55 yr, but may present in pre-menopausal women<br>Often coexists with benign leiomyomata (fibroids) | Histologic distinction from leiomyoma<br>1. Increased mitotic count (>10 mitoses/10 high-power fields)<br>2. Tumour necrosis<br>3. Cellular atypia<br>Rapidly enlarging fibroids in a pre-menopausal woman<br>Enlarging fibroids in a postmenopausal woman | Often post-operatively after uterus removed for presumed fibroids<br>Stage using FIGO 2009 staging for leiomyosarcomas and ECC | Hysterectomy/BSO usually<br>No routine pelvic lymphadenectomy<br>Chemotherapy is used in cases of metastatic disease<br>Radiation therapy does not improve local control or survival<br>Poor outcomes overall, even for early-stage disease |
| **2. Endometrial Stromal Sarcoma (ESS)** | Usually presents in perimenopausal or postmenopausal women with abnormal uterine bleeding | Abnormal uterine bleeding<br>Good prognosis | Diagnosed by histology of endometrial biopsy or D&C<br>Stage using FIGO 2009 staging for leiomyosarcomas and ECC | Hysterectomy & BSO (remove ovaries as ovarian hormones may stimulate growth)<br>No routine pelvic lymphadenectomy<br>Adjuvant therapy based on stage and histologic features (hormones and/or radiation)<br>Hormonal therapy (progestins) may be used for metastatic disease |
| **3. Undifferentiated Sarcoma** | Rare; less common than leiomyosarcoma, endometrial stromal sarcoma | Severe nuclear pleomorphism, high mitotic activity, tumour cell necrosis, and lack smooth muscle or endometrial stromal differentiation<br>Poor prognosis | Often found incidentally post-operatively for abnormal bleeding | Treatment primarily surgical<br>Radiation and/or chemotherapy for advanced diseased or unresectable disease |
| **MIXED TYPE** | | | | |
| **4. Adenosarcoma** | The rarest of the uterine sarcoma<br>Mixed tumour of low malignancy potential | Present with abnormal vaginal bleeding<br>Polypoid mass in uterine cavity | Mixture of benign epithelium with malignant low-grade sarcoma<br>Often found incidentally at time of hysterectomy for PMB<br>Stage using FIGO 2009 staging for adenosarcoma | Treatment is surgical with hysterectomy and BSO |

**Table 24. FIGO Staging of Uterine Sarcoma (2009)**

| Stage | Description | Stage | Description |
|---|---|---|---|
| **I** | **Tumour limited to uterus** | **III** | |
| IA | <5 cm | IIIA | Tumour invades abdominal tissues, one site |
| IB | >5 cm | IIIB | Metastasis to pelvic and/or para-aortic lymph nodes |
| | | IIIC | Tumour invades bladder and/or rectum |
| **II** | **Tumour extends beyond uterus** | **IV** | |
| IIA | To the pelvis, adnexal involvement | IVA | Tumour invades bladder and/or rectum |
| IIB | To extra-uterine pelvic tissue | IVB | Distant metastasis |

# Ovary

## BENIGN OVARIAN TUMOURS

- see Table 25
- many are asymptomatic
- usually enlarge slowly, if at all
- may rupture or undergo torsion, causing pain
  - pain associated with torsion of an adnexal mass usually originates in the iliac fossa and radiates to the flank
- peritoneal irritation may result from an infarcted tumour (rare)

## MALIGNANT OVARIAN TUMOURS

- see Table 25

### Epidemiology

- lifetime risk 1.4%
- in women >50 yr, more than 50% of ovarian tumours are malignant
- causes more deaths in North America than all other gynecologic malignancies combined
- 4th leading cause of cancer death in women
- 85% epithelial; 15% non-epithelial
- 10-15% of epithelial ovarian cancers are related to hereditary predisposition

### Risk Factors (for epithelial ovarian cancers)

- early menarche and/or late menopause
- personal history of breast, colon, endometrial cancer
- family history of breast, colon, endometrial, ovarian cancer
- Lynch syndrome and BRCA mutations
- use of fertility drugs

### Protective Factors (for epithelial ovarian cancers)

- OCP: likely due to ovulation suppression (significant reduction in risk even after 1 yr of use)
- pregnancy/breastfeeding

### Prophylactic Measures

- salpingectomy (prophylactic)
- BSO (prophylactic hysterectomy or tubal ligation performed for this reason in high-risk women [i.e. BRCA mutation carriers])

### Screening

- no effective method of mass screening
- routine CA-125 level measurements or U/S not recommended
  - high false positive rates
- controversial in high-risk groups: transvaginal U/S and CA-125, starting age 30 (no consensus on interval)
  - familial ovarian cancer (>1 first degree relative affected, BRCA-1 mutation)
  - other cancers (e.g. endometrial, breast, colon)
  - BRCA-1 or BRCA-2 mutation: recommendation is prophylactic bilateral oophorectomy after age 35 or when childbearing is completed

### Clinical Features

- most women with epithelial ovarian cancer present with advanced stage disease as patients often asymptomatic until disseminated (symptoms with early-stage disease are vague and non-specific)
- when present, symptoms may include:
  - abdominal symptoms (nausea, bloating, pain, dyspepsia, anorexia, early satiety)
  - symptoms of mass effect
    - increased abdominal girth (from ascites or tumour itself)
    - urinary urgency and frequency
    - constipation



**Ovaries are like GEMS**
**G**erm-cell
**E**pithelial
**M**etastatic
**S**ex cord stromal



Most (70%) epithelial ovarian cancers present at stage III disease



**Ovarian Tumour Markers**
- Epithelial cell: CA-125
- Stromal
- Granulosa cell: inhibin
- Sertoli-Leydig: androgens
- Germ cell
- Dysgerminoma: LDH
- Yolk sac: AFP
- Choriocarcinoma: β-hCG
- Immature teratoma: none
- Embryonal cell: AFP + β-hCG



Diagnosis of ovarian tumours requires surgical pathology



Any adnexal mass in postmenopausal women should be considered malignant until proven otherwise



**Omental Cake**: a term for ascites plus a fixed upper abdominal and pelvic mass; almost always signifies ovarian cancer



**Malignant Ovarian Tumour Prognosis**
**5 Year Survival**

| | |
|---|---|
| Stage I | 75-95% |
| Stage II | 60-75% |
| Stage III | 23-41% |
| Stage IV | 11% |



**Screening for Ovarian Cancer Updated Evidence Report and Systematic Review for the US Preventive Services Task Force**
JAMA 2018; 319(6):595-606
**Objective**: To systematically review evidence on benefits and harms of ovarian cancer screening among average-risk, asymptomatic women.
**Methods**: Systematic review of RCTs of ovarian cancer screening in average-risk women that reported mortality or quality-of-life outcomes. Interventions included transvaginal ultrasound and/or CA-125 testing. Comparators were usual care or no screening.
**Results**: Four trials (N = 293 587) were included. No trial found a significant difference in ovarian cancer mortality with screening. In 2 trials, screening led to surgery for suspected ovarian cancer in 1% of women without cancer and in 3% for transvaginal ultrasound with or without CA-125 screening, with major complications occurring in 3% to 15% of surgeries. Evidence of psychological harms was found in cases of repeat follow-up scans and tests.
**Conclusions**: Ovarian cancer mortality did not significantly differ between screened women and those with no screening or in usual care.

## Low Malignant Potential (also called "Borderline") Tumours

- a subcategory of epithelial ovarian cancer (~15% of all epithelial ovarian tumours)
- pregnancy, OCP, and breastfeeding are protective factors
- tumour cells with histologically malignant characteristics arise from the ovarian surface, but do not invade ovarian stroma
- able to metastasize, but not commonly
- treated primarily with surgery (BSO/omental biopsy ± hysterectomy)
  - chemotherapy has limited benefit: can be treated with hormonal manipulation (letrozole)
- generally slow growing, excellent prognosis
  - 5 yr survival >99%
  - recurrences tend to occur late, may be associated with low-grade serous carcinoma

### Table 25. Ovarian Tumours

| Type | Description | Presentation | Ultrasound/Cytology | Treatment |
|---|---|---|---|---|
| **FUNCTIONAL TUMOURS (all benign)** | | | | |
| **Follicular Cyst** | Follicle fails to rupture during ovulation | Usually asymptomatic<br>May rupture, bleed, tort, infarct causing pain ± signs of peritoneal irritation | 4-8 cm mass, unilocular, lined with granulosa cells | Symptomatic or suspicious masses warrant surgical exploration<br>Otherwise if <6 cm, wait 6 wk then re-examine as cyst usually regresses with next cycle<br>OCP (ovarian suppression): will prevent development of new cysts<br>Treatment usually laparoscopic (cystectomy vs. oophorectomy, based on fertility choice) |
| **Corpus Luteum Cyst** | Corpus luteum fails to regress after 14 d, becoming cystic or hemorrhagic | More likely to cause pain than follicular cyst<br>May delay onset of next period | Larger (10-15 cm) and firmer than follicular cysts | Same as for follicular cysts |
| **Theca-Lutein Cyst** | Due to atretic follicles stimulated by abnormal β-hCG levels | Associated with molar pregnancy, ovulation induction with clomiphene | | Conservative<br>Cyst will regress as β-hCG levels fall |
| **Endometrioma** | See *Endometriosis*, GY11 | | | |
| **Polycystic Ovaries** | See *Polycystic Ovarian Syndrome*, GY23 | | | |
| **BENIGN GERM-CELL TUMOURS** | | | | |
| **Benign Cystic Teratoma (dermoid)** | Single most common ovarian germ cell neoplasm<br>Elements of all 3 cell lines; contains dermal appendages (sweat and sebaceous glands, hair follicles, teeth) | May rupture, twist, infarct<br>20% bilateral<br>20% occur outside of reproductive yr | Smooth-walled, mobile, unilocular<br>Ultrasound may show calcification which is pathognomonic | Treatment usually laparoscopic cystectomy; may recur |
| **MALIGNANT GERM-CELL TUMOURS** | | | | |
| **General Information** | Rapidly growing, 2-3% of all ovarian cancers | Usually children and young women (<30 yr) | | Surgical resection (often conservative unilateral salpingo-oophorectomy ± nodes) ± chemotherapy |
| **Dysgerminoma** | Produces LDH | 10% bilateral | | When diagnosed at stage IA, no adjuvant treatment is indicated<br>If diagnosed at advanced stage, very responsive to chemotherapy, therefore complete resection is not necessary for cure |
| **Immature Teratoma** | No tumour marker identified | Almost always unilateral | | When diagnosed at stage IA Grade 1, no adjuvant treatment is indicated<br>When diagnosed at Grade 2-3, either adjuvant chemotherapy or surgical staging<br>If diagnosed at advanced stage, very responsive to chemotherapy, therefore complete resection is not necessary for cure |
| **Yolk Sac Tumour** | Produces AFP | Abdominal pain and pelvic mass | | When diagnosed at stage IA Grade 1, no adjuvant treatment is indicated<br>If diagnosed at advanced stage, very responsive to chemotherapy, therefore complete resection is not necessary for cure |
| **Ovarian Choriocarcinoma** | Produces hCG | Precocious puberty and irregular vaginal bleeding | | When diagnosed at stage IA Grade 1, no adjuvant treatment is indicated<br>If diagnosed at advanced stage, very responsive to chemotherapy, therefore complete resection is not necessary for cure |
| **EPITHELIAL OVARIAN TUMOURS (malignant or borderline)** | | | | |
| **General Information** | Derived from mesothelial cells lining peritoneal cavity<br>Classified based on histologic type<br>80-85% of all ovarian neoplasms (includes malignant) | | Varies depending on subtype | **Borderline**<br>Cystectomy vs. unilateral salpingo-oophorectomy<br>**Malignant**<br>1. Early stage (stage I): Hysterectomy/BSO/staging (omentectomy, peritoneal biopsies, washings, pelvic and para-aortic lymphadenectomy)<br>2. Advanced stage: Upfront cytoreductive (debulking) followed by adjuvant chemotherapy consisting of IV carboplatic/paclitaxel vs. intraperitoneal chemotherapy (stage III) neoadjuvant chemotherapy with IV carboplatin/paclitaxel, followed by delayed debulking with further adjuvant IV chemotherapy |
| **Serous** | Most common ovarian tumour<br>50% of all ovarian cancers<br>75% of epithelial tumours<br>70% benign | 20-30% bilateral | Lining similar to fallopian tube epithelium<br>Often multilocular<br>Histologically contain Psamomma bodies (calcified concentric concretions) | |

**Table 25. Ovarian Tumours** (continued)

| Type | Description | Presentation | Ultrasound/Cytology | Treatment |
|---|---|---|---|---|
| **EPITHELIAL OVARIAN TUMOURS (malignant or borderline)** | | | | |
| **Mucinous** | 20% of epithelial tumours | Rarely complicated by Pseudomyxoma peritoneii: implants seed abdominal cavity and produce large quantities of mucin | Resembles endocervical epithelium<br>Often multilocular<br>May reach enormous size | Poor response to chemotherapy<br>If mucinous, remove appendix as well to rule out possible source of primary disease |
| **SEX CORD STROMAL OVARIAN TUMOURS** | | | | |
| **General Information** | | | | Surgical resection of tumour<br>Chemotherapy may be used for unresectable metastatic disease |
| **Fibroma/Thecoma (benign)** | From mature fibroblasts in ovarian stroma | Non-functioning<br>Occasionally associated with Meig's syndrome (benign ovarian tumour and ascites and pleural effusion) | Firm, smooth rounded tumour with interlacing fibrocytes | |
| **Granulosa-Theca Cell Tumours (benign or malignant)** | Can be associated with endometrial cancer<br>Inhibin is tumour marker | Estrogen-producing: feminizing effects (precocious puberty, menorrhagia, postmenopausal bleeding) | Histologic hallmark of cancer is small groups of cells known as Call-Exner bodies | |
| **Sertoli-Leydig Cell Tumour (benign or malignant)** | Can measure elevated androgens as tumour markers | Androgen-producing: virilizing effects (hirsutism, deep voice, recession of front hairline) | | |
| **METASTATIC OVARIAN TUMOURS** | | | | |
| **From GI Tract, Breast, Endometrium, Lymphoma** | 4-8% of ovarian malignancies<br>Krukenberg tumour – metastatic ovarian tumour (usually GI tract, commonly stomach or colon, breast) with "signet-ring" cells | | | |

## Investigation of Suspicious Ovarian Mass

- women with suspected ovarian cancer based on history, physical, or investigations should be referred to a gynecologic oncologist
  - bimanual examination
    - solid, irregular, or fixed pelvic mass is suggestive of ovarian cancer
  - RMI (Risk of Malignancy Index) is best tool available to assess likelihood of ovarian malignancy and need for pre-operative gynecologic oncology referral (see sidebar)
- physical exam findings largely dependent on stage of disease
- blood work: CA-125 for baseline, CBC, liver function tests, electrolytes, creatinine
- radiology
  - transvaginal ultrasound best to visualize ovaries
  - CT abdomen and pelvis to look for metastatic disease
  - bone scan or PET scan not indicated
- try to rule out other primary source if suspected, based on:
  - occult blood per rectum: endoscopy ± barium enema
  - gastric symptoms: gastroscopy ± upper GI series
  - abnormal vaginal bleeding: endometrial biopsy to rule out concurrent endometrial cancer; abnormal cervix: need to biopsy cervix (not Pap smear); breast lesion identified or risk factors present: mammogram



**A Risk of Malignancy Incorporating CA-125, Ultrasound, and Menopausal Status for the Accurate Pre-Operative Diagnosis of Ovarian Cancer**
BJOG 1990;97:922-29
RMI = U x M x CA-125
**Ultrasound Findings (1 pt for each)**
- Multilocular cyst
- Evidence of solid areas
- Evidence of metastases
- Presence of ascites
- Bilateral lesions

U = 1 (for U/S scores of 0 or 1)
U = 4 (for U/S scores of 2-5)
**Menopausal Status**
- Postmenopausal: M = 4
- Premenopausal: M = 1

**Absolute Value of CA-125 Serum Level**
- For RMI>200: gynecologic oncology referral is recommended

**Table 26. FIGO Staging for Primary Carcinoma of the Ovary (Surgical Staging) (2014)**

| Stage | Description |
|---|---|
| I | **Growth limited to the ovaries** |
| IA | 1 ovary, no ascites, no tumour on external surface, capsule intact, negative washings |
| IB | 2 ovaries, no ascites, no tumour on external surface, capsule intact |
| IC | 1 or 2 ovaries with any of the following: surgical spill (IC1), capsule ruptured (IC2), tumour on ovarian surface (IC2), or malignant cells in ascites (IC3) |
| **II** | **Growth involving one or both ovaries with pelvic extension or primary peritoneal cancer** |
| IIA | Extension ± implants to uterus/tubes |
| IIB | Extension to other pelvic structures |
| **III** | **Tumour involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal nodes** |
| IIIA | Positive retroperitoneal LNs and/or microscopic metastasis beyond pelvis |
| IIIA1 | Positive retroperitoneal LNs |
| IIIA2 | Microscopic, extrapelvic peritoneal involvement ± positive retroperitoneal LNs |
| IIIB | Macroscopic peritoneal metastasis beyond pelvis ≤2 cm, ± positive retroperitoneal LNs. Includes extension to capsule of liver/spleen |
| IIIC | Same as above but peritoneal metastasis >2 cm |
| **IV** | **Distant metastasis beyond peritoneal cavity** |
| **IVA** | Pleural effusion with positive cytology |
| **IVB** | Hepatic and/or splenic parenchymal metastasis or metastasis to extra-abdominal organs (inguinal LNs and LNs outside of abdominal cavity included) |

FIGO = International Federation of Gynecology and Obstetrics

# Fallopian Tube

- least common site for carcinoma of female reproductive system (0.3%)
- usually serous epithelial carcinoma
- new evidence shows that some serous ovarian cancers originate in the fallopian tube
- more common in fifth and sixth decade

### Clinical Features
- classic triad present in minority of cases, but very specific
  - watery discharge (most specific): "hydrops tubae profluens"
  - vaginal bleeding or discharge in 50% of patients
  - crampy lower abdominal/pelvic pain
  - most patients present with a pelvic mass (see *Ovarian Tumours*, GY41 for guidelines regarding diagnosis/investigation)

### Treatment
- as for malignant epithelial ovarian tumours

**Effectiveness, Safety, and Cost-Effectiveness of Primary Cytoreductive Surgery**
Cochrane Database Syst *Rev* 2011;(8):CD007565
**Summary**: During primary surgery for stage III or IV epithelial ovarian cancer, all attempts should be made to achieve complete cytoreduction. When this is not achievable, optimal (<1cm) residual disease should be the goal.
**Methods**: Identified 11 retrospective studies consisting of 4735 women using comprehensive search strategy.
**Results:**
1. When suboptimal (margins >1cm) was compared with optimal (<1cm) cytoreduction, the survival estimates were reduced but remained statistically in favour of the lower volume disease group
2. No significant difference in overall survival between suboptimal and optimal cytoreduction
3. Borderline difference in progression-free survival when residual disease >2 cm and <2 cm were compared (p=0.05)

# Cervix

## BENIGN CERVICAL LESIONS
- Nabothian cyst/inclusion cyst: no treatment required
- endocervical polyps: treatment is polypectomy (office procedure)

## MALIGNANT CERVICAL LESIONS

### Epidemiology
- majority are SCC (95%); adenocarcinomas increasing (5%); rare subtypes include small cell, adenosquamous
- 8000 deaths annually in North America
- annual Pap test reduces a woman's chance of dying from cervical cancer from 0.4% to 0.05%
- average age at presentation: 52 yr old

### Etiology
- at birth, vagina is lined with squamous epithelium; columnar epithelium lines only the endocervix and the central area of the ectocervix (original squamocolumnar junction)
- during puberty, estrogen stimulates eversion of a single columnar layer (ectopy), thus exposing it to the acidic pH of the vagina, leading to metaplasia (change of exposed epithelium from columnar to squamous)
  - a new squamocolumnar junction forms as a result
- the transformation zone (TZ) is the area located between the original and the current squamocolumnar junction
- the majority of dysplasias and cancers arise in the TZ of the cervix
- must have active metaplasia in presence of inducing agent (HPV) to get dysplasia
- dysplasia progresses to carcinoma in situ (CIS), which further progresses to invasion
- slow process (~10 yr on average)
- growth is by local extension
- metastasis occurs late

### Risk Factors
- HPV infection
  - see *Sexually Transmitted Infections*, GY26
  - high risk of neoplasia associated with types 16, 18
  - low risk of neoplasia associated with types 6, 11
  - >99% of cervical cancers contain one of the high risk HPV types
- high-risk behaviours (risk factors for HPV infection)
  - multiple partners
  - other STIs (HSV, trichomonas)
  - early age at first intercourse
  - high-risk male partner
- smoking
- poor screening uptake is the most important risk factor for cervical cancer in Canada
- at-risk groups include:
  - immigrant Canadians
  - First Nations Canadians
  - geographically-isolated Canadians
  - sex-trade workers
  - low socioeconomic status Canadians

### Cervical Cancer Screening Guidelines (Pap Test)
- see Family Medicine, FM5

**Causes of Elevated CA-125**
- Age influences reliability of test as a tumour marker
- 50% sensitivity in early-stage ovarian cancer (poor), therefore not good for screening

**Malignant**
- Gyne: ovary, uterus
- Non-Gyne: pancreas, stomach, colon, rectum

**Non-Malignant**
- Gyne: benign ovarian neoplasm, endometriosis, pregnancy, fibroids, PID
- Non-Gyne: cirrhosis, pancreatitis, renal failure

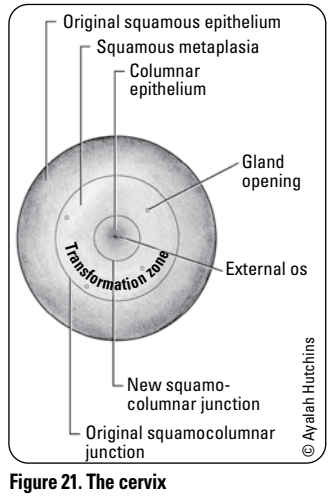



**Figure 21. The cervix**

Cervical cancer is most prevalent in developing countries and, therefore, is the only gynecologic cancer that uses clinical staging; this facilitates consistent international staging with countries that do not have technologies, such as CT and MRI

## Clinical Features

- SCC: exophytic, fungating tumour
- adenocarcinoma: endophytic, with barrel-shaped cervix
- early
  - asymptomatic
  - discharge: initially watery, becoming brown or red
  - postcoital bleeding
- late
  - 80-90% present with bleeding: either postcoital, postmenopausal or irregular bleeding
  - pelvic or back pain (extension of tumour to pelvic walls)
  - bladder/bowel symptoms
- signs
  - friable, raised, reddened, or ulcerated area visible on cervix

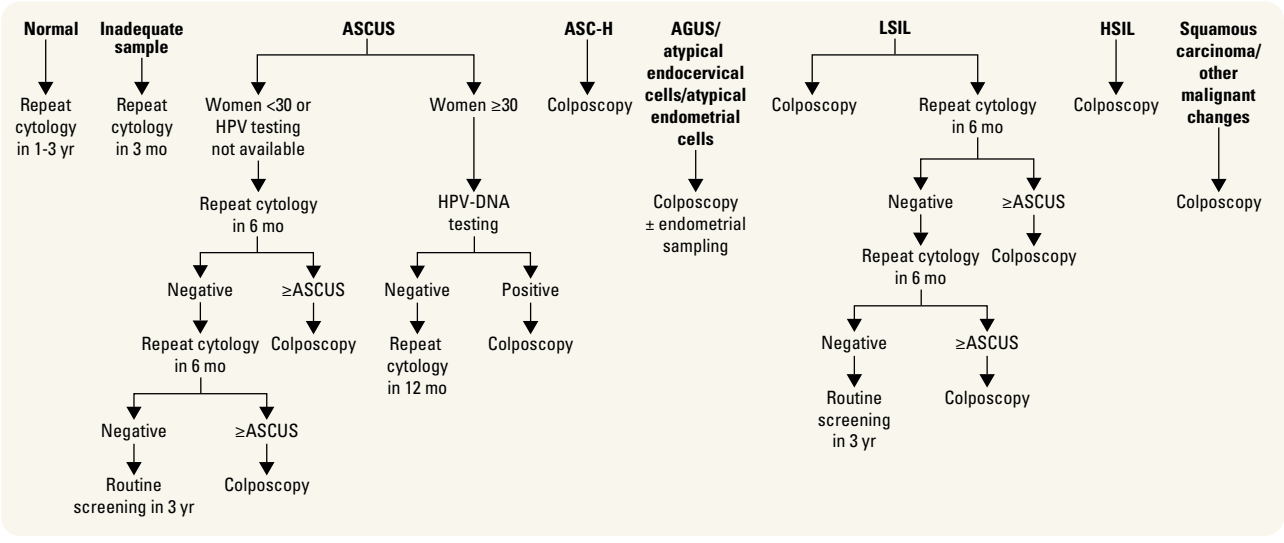



**Figure 22. Decision making chart for Pap test (not applicable for adolescents)**
Adapted from: Ontario Cervical Screening Practice Guidelines. May 2012. Cervical screening guidelines unique to each province

## Diagnosis

- colposcopy is a clinical procedure that facilitates identification and biopsy of suspicious cells
- in colposcopy:
  - apply acetic acid and identify acetowhite lesions, punctation, mosaicism, and abnormal blood vessels to guide cervical biopsy
  - endocervical curettage (ECC) if entire lesion is not visible or no lesion visible
  - diagnostic excision (LEEP) if:
    - unsatisfactory colposcopy (poor visualization/access to transformation zone)
    - discrepancy between cytology, colposcopy, and histological findings
    - positive findings/glandular abnormalities in endocervical curettage
    - suspicious for adenocarcinoma in situ (consider cold-knife conization)
    - recurrence of lesion post-ablation or excision
    - inability to rule out invasive disease, i.e. large lesions (lesions extending into endocervical canal, extending widely on cervix, or onto vaginal epithelium)
- consider cold-knife conization (in OR) if glandular abnormality suspected based on cytology or colposcopic findings due to concern for margin interpretation
- tests permitted for FIGO clinical staging include: physical exam (including examination under anesthesia), cervical biopsy (including cone biopsy), proctoscopy/cystoscopy, intravenous pyelogram, ultrasound liver/kidneys, CXR, LFTs
- MRI and/or CT and/or PET scan often done to facilitate planning of radiation therapy, results do not influence clinical stage



**The Bethesda Classification System** is based on cytological results of a Pap test that permits the examination of cells but not tissue structure. Cervical intraepithelial neoplasia (CIN) or cervical carcinoma is a histological diagnosis, requiring a tissue sample via biopsy of suspicious lesions seen during colposcopy



With development of hypertension early in pregnancy (i.e. <20 wk), think gestational trophoblastic disease



CA-125 is indicated for monitoring response to treatment

**Table 27. FIGO Staging Classification of Cervical Cancer (Clinical Staging) (2018)**

| Stage | Description |
|---|---|
| **I** | **Confined to cervix** |
| IA | Microinvasive (diagnosed only by microscopy) |
| IA1 | Stromal invasion not >3 mm deep, not >7 mm wide |
| IA2 | 3-5 mm deep; not >7 mm wide |
| IB | Clinically visible lesion confined to cervix, or microscopic lesion >IA |
| IB1 | Clinically visible lesion ≤4 mm in greatest dimension |
| IB2 | Clinically visible lesion >4 mm in greatest dimension |
| **II** | **Beyond uterus but not to the pelvic wall or lower 1/3 of vagina** |
| IIA | No obvious parametrial involvement |
| IIA1 | Clinically visible lesion ≤4 mm in greatest dimension |
| IIA2 | Clinically visible lesion >4 mm in greatest dimension |
| IIB | Obvious parametrial involvement |
| **III** | **Extends to pelvic wall, and/or involves lower 1/3 of vagina and/or causes hydronephrosis or non-functioning kidney** |
| IIIA | Involves lower 1/3 vagina but no extension into pelvic side wall |
| IIIB | Extension into pelvic side wall and/or hydronephrosis or non-functioning kidney |
| **IV** | **Carcinoma has extended beyond true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum** |
| IVA | Spread of the growth to adjacent organs (bladder or rectum) |
| IVB | Distant metastases |

## Treatment: Prevention and Management

### Prevention: HPV Vaccine

- two vaccines currently approved (Gardasil®, Cervarix®)

**Table 28. Comparison of Two Vaccines against Human Papillomavirus (HPV)**

| | Gardasil®* | Cervarix® |
|---|---|---|
| **Viral Strains Covered** | 6, 11, 16, 18 | 16, 18 |
| **Route of Administration** | IM | IM |
| **Schedule of Dosing** | 0, 2, 6 mo | 0, 1, 6 mo |
| **Side Effects** | Local: redness, pain, swelling<br>General: headache, low grade fever, GI upset | Local: redness, pain, swelling<br>General: headache, low grade fever, GI upset |
| **Approved Age** | Females age 9-45, males age 9-26 | Females age 10-25 |
| **Contraindications** | Pregnant women and women who are nursing (limited data) | |

*Gardasil-9 also covers types 31, 33, 45, 52, and 58; also used to prevent genital wards

- should be administered before onset of sexual activity (i.e. before exposure to virus) for optimal benefit of vaccination
- may be given at the same time as hepatitis B or other vaccines using a different injection site
- not for treatment of active infections
- most women will not be infected with all four types of the virus at the same time, therefore vaccine is still indicated for sexually active females or those with a history of previous HPV infection or HPV-related disease
- conception should be avoided until 30 d after last dose of vaccination



**Causes of Elevated CA-125**

- Age influences reliability of test as a tumour marker
- 50% sensitivity in early stage ovarian cancer (poor) – therefore not good for screening

**Malignant**

- Gyne: ovary, uterus
- Non-Gyne: pancreas, stomach, colon, rectum

**Non-Malignant**

- Gyne: benign ovarian neoplasm, endometriosis, pregnancy, fibroids, PID
- Non-Gyne: cirrhosis, pancreatitis, renal failure



**Cervical Cancer Prognosis 5 yr Survival**

| | |
|---|---|
| Stage 0 | 99% |
| Stage I | 75% |
| Stage II | 55% |
| Stage III | 30% |
| Stage IV | 7% |
| Overall | 50-60% |



**Efficacy of Human Papillomavirus (HPV)-16/18 AS04-Adjuvanted Vaccine Against Cervical Infection and Precancer Caused by Oncogenic HPV Types (PATRICIA): Final Analysis of a Double-Blind, Randomized Study in Young Women**

Lancet 2009;374:301-14

**Study**: Phase III double-blind, controlled RCT.

**Patients**: 18,644 women aged 15-25.

**Selected Outcomes**: Development of HPV-16/18 associated CIN II+ was the primary outcome. Secondary to this were persistence of infections with HPV-16, HPV-18, or other oncogenic HPV types.

**Selected Results**: Efficacy against development of HPV-16/18 associated CIN II+ was 98.1% ($p<0.0001$). High levels of cross-protection were observed for persistent infection with HPV-31 and HPV-45 and HPV-31 or HPV-45 associated CIN II+.

**Conclusions**: The HPV-16/18 AS04-adjuvanted vaccine protected against HPV-16/18 associated CIN II+ lesions and lesions associated with HPV-31, HPV-33, and HPV-45.

**Table 29. Management of Abnormal Cervical Histology and Cervical Cancer**

| | Management |
|---|---|
| **CIN I** | Preferred option for biopsy-proven CIN I is observation<br>Repeat assessment and cytology in 12 mo<br>Management according to cytology results<br>If after HSIL or AGC:<br>Cytology and histology should be reviewed<br>If discrepancy remains, excisional biopsy may be considered |
| **CIN II and CIN III** | Women ≥25 yr<br>CIN II or III should be treated<br>Excisional procedures preferred for CIN III<br>Those with positive margins should have follow-up with colposcopy and directed biopsies and/or endocervical curettage<br>Women <25 yr<br>Same treatment for CN II and CN III: observe with colposcopy at 6-mo intervals for up to 24 mo before treatment considered<br>During pregnancy<br>CIN II or III suspected or diagnosed during pregnancy: repeat colposcopy and treatment delayed until 8-12 wk after delivery |
| **Stage IA1 (no LVSI)** | LEEP if future fertility desired (and lesion ≤2 cm)<br>Simple hysterectomy if future fertility is not desired |
| **Stage IA2, IB1** | Typically treated with radical hysterectomy and pelvic lymphadenectomy (sentinel nodes under study)<br>If high chance of adjuvant radiation then consider primary chemoradiation as more morbidity occurs from double-modality treatment (surgery and radiation)<br>Equal cure rates may be obtained with primary radiation therapy; advantage of surgery: may accurately stage and grade and more targeted adjuvant therapy<br>Advantage is that ovaries can be spared if pre-menopausal<br>For fertility preservation (if tumour <2 cm), may have radical trachelectomy (removal of cervix and parametria) and nodes instead of radical hysterectomy for early-stage disease<br>Chemoradiation therapy if adverse high-risk prognostic factors on radical surgical specimen, such as: positive pelvic lymph nodes, positive parametria, and/or positive margins or adverse cervical factors (2 or more): deep stromal invasion, size >4 cm, LVSI |
| **Stages IB2 (>4 cm), II, III, IV** | Primary chemoradiation therapy<br>CT assess extent of disease: evaluate pelvic and para-aortic nodes<br>For positive nodes on PET: primary chemoradiation with extended field RT<br>Hysterectomy generally not suggested following primary treatment with curative intent |

### Abnormal Pap Tests in Pregnancy

- incidence: 1/2200
- Pap test at all initial prenatal visits
  - if abnormal Pap or suspicious lesion, refer to colposcopy
  - if diagnostic conization required, should be deferred until second trimester (T2) to minimize risk of pregnancy loss
  - if invasive cancer ruled out, management of dysplasia deferred until completion of pregnancy (may deliver vaginally)
  - if invasive cancer present, management depends on prognostic factors, degree of fetal maturity, and patient wishes
    - general recommendations in T1: consider pregnancy termination, management with either radical surgery (hysterectomy vs. trachelectomy if desires future fertility), or concurrent chemoradiation therapy
    - recommendations in T2/T3: delay of therapy until viable fetus and C-sectionfor delivery with concurrent radical surgery or subsequent concurrent chemoradiation therapy

# Vulva

## BENIGN VULVAR LESIONS

### Non-Neoplastic Disorders of Vulvar Epithelium

- biopsy is necessary to make diagnosis and/or rule out malignancy:

1) Hyperplastic dystrophy (squamous cell hyperplasia)
   - surface thickened and hyperkeratotic
   - pruritus most common symptom
   - typically postmenopausal women
   - treatment: 1% fluorinated corticosteroid ointment bid for 6 wk
2) Lichen sclerosis
   - subepithelial fat becomes diminished; labia become thin, atrophic, with membrane-like epithelium and labial fusion
   - pruritus, dyspareunia, burning
   - 'figure of 8' distribution
   - most common in postmenopausal women but can occur at any age
   - treatment: ultrapotent topical steroid 0.05% clobetasol x 2-4 wk then taper down, can consider long-term suppression twice a week
3) Mixed dystrophy (lichen sclerosis with epithelial hyperplasia)
   - hyperkeratotic areas with areas of thin, shiny epithelium
   - treatment: fluorinated corticosteroid ointment

### Tumours
- papillary hidradenoma, nevus, fibroma, hemangioma

## MALIGNANT VULVAR LESIONS

### Epidemiology
- 5% of genital tract malignancies
- 90% SCC; remainder melanomas, basal cell carcinoma, Paget's disease, Bartholin's gland carcinoma
  - Type I disease: HPV-related (50-70%)
    - more likely in younger women
    - 90% of vulvar intraepithelial neoplasia (VIN) contain HPV DNA (usually types 16, 18)
  - Type II disease: not HPV-related, associated with current or previous vulvar dystrophy
    - usually postmenopausal women

### Risk Factors
- HPV infection
- VIN: precancerous change which presents as multicentric white or pigmented plaques on vulva (may only be visible at colposcopy)
  - progression to cancer rarely occurs with appropriate management
  - treatment: local excision (i.e. superficial vulvectomy ± split thickness skin grafting to cover defects if required) vs. ablative therapy (i.e. laser, cauterization) vs. local immunotherapy (imiquimod)
- history of cervical cancer
- cigarette smoking
- immunodeficiency

### Clinical Features
- many patients asymptomatic at diagnosis (many also deny or minimize symptoms)
- most lesions occur on the labia majora, followed by the labia minora (less commonly on the clitoris or perineum)
- localized pruritus or lesion most common
- less common: raised red, white or pigmented plaque, ulcer, bleeding, discharge, pain, dysuria
- patterns of spread
  - local
  - groin lymph nodes (usually inguinal, then spreading to pelvic nodes)
  - hematogenous

### Investigations
- ± vulvar biopsy
- always biopsy any suspicious lesion
  - do not remove entire lesion (allows for site identification through sentinel LN injection if malignant)



Any suspicious lesion of the vulva should be biopsied

### Prognosis
- depends on stage: particularly nodal involvement (single most important predictor followed by tumour size)
- lesions >4 cm associated with poorer prognosis
- overall 5 yr survival rate: 79%

### Treatment
- T1 lesions (tumour confined to vulva; no extension to adjacent perineal structures): radical local excision
- T2 lesions (tumour of any size with extension to adjacent perineal structures): modified radical vulvectomy
- T3 lesions (extension to any of: proximal 2/3 of urethra, proximal 2/3 of the vagina, bladder mucosa, rectal mucosa, or fixed to pelvic bone): chemoradiation followed by selective resection of residual primary
- node positive disease: adjuvant chemoradiation or radiation therapy

# Vagina

## BENIGN VAGINAL LESIONS

- inclusion cysts
  - cysts form at site of abnormal healing of laceration (e.g. episiotomy)
  - no treatment required
- endometriosis
  - dark lesions that tend to bleed at time of menses
  - treatment: excision
- Gartner's duct cysts
  - remnants of Wolffian duct, seen along side of cervix
  - treatment: conservative unless symptomatic
- urethral diverticulum
  - can lead to recurrent urethral infection, dyspareunia
  - treatment: surgical correction if symptomatic

## MALIGNANT VAGINAL LESIONS

### Epidemiology

- primary carcinomas of the vagina represent 2-3% of malignant neoplasms of the female genital tract
- 80-90% are SCC
- more than 50% diagnosed between 70-90 yr old

### Risk Factors

- associated with HPV infection (analogous to cervical cancer)
- increased incidence in patients with prior history of cervical and vulvar cancer

### Investigations

- cytology
  - significant false negative rate for existing malignancy (i.e. if gross lesion present, biopsy)
- colposcopy
- Schiller test (normal squamous epithelium takes up Lugol's iodine)
- biopsy, partial vaginectomy (wide local excision for diagnosis)
- rule out disease on cervix, vulva, or anus (most vaginal cancers are metastatic from one of these sites)
- staging

### Clinical Features

**Table 30. Clinical Features of Malignant Vaginal Lesions**

| Type | Clinical Features |
|---|---|
| **Vaginal Intra-Epithelial Neoplasia (VAIN)** | Grades: analogous to cervical dysplasia |
| **Squamous Cell Carcinoma (SCC)** | Most common site is upper 1/3 of posterior wall of vagina<br>Asymptomatic<br>Painless discharge and bleeding<br>Vaginal discharge (often foul-smelling)<br>Vaginal bleeding especially during/post-coitus<br>Urinary and/or rectal symptom 2° to compression |
| **Adenocarcinoma** | Most are metastatic, usually from cervix, endometrium, ovary, or colon<br>Most primaries are clear-cell adenocarcinomas<br>2 types: non-DES and DES syndrome |

### Treatment

- Stage I
  - radiation therapy: for tumours >2 cm diameter or tumour involvement of the mid- to low-grade vagina
  - surgical excision: radical hysterectomy, upper vaginectomy, and bilateral pelvic lymphadenectomy
- Stage II-IV: chemoradiation

# Gestational Trophoblastic Disease/Neoplasia

- refers to a spectrum of proliferative abnormalities of the trophoblast

## Epidemiology
- 1/1000 pregnancies
- marked geographic variation (as high as 1/125 in Taiwan)
- 80% benign, 15% locally invasive, 5% metastatic
- cure rate >95%

## HYDATIDIFORM MOLE (Benign GTD)

### Complete Mole
- most common type of hydatidiform mole
- diffuse trophoblastic hyperplasia, hydropic swelling of chorionic villi, no fetal tissues or membranes present
- 46XX or 46XY, chromosomes completely of paternal origin (90%)
- 2 sperm fertilize empty egg or 1 sperm with reduplication
- 15-20% risk of progression to malignant sequelae
- risk factors
  - geographic (South East Asia most common)
  - others (maternal age >40 yr, β-carotene deficiency, vitamin A deficiency not proven)
- clinical features often present during apparent pregnancy with abnormal symptoms/findings
  - vaginal bleeding (97%)
  - hyperemesis gravidarum (26%)
  - excessive uterine size for LMP (51%)
  - hyperthyroidism (7%)
  - theca-lutein cysts >6 cm (50%)
  - β-hCG >100,000 IU/L
  - preeclampsia (27%)
  - no fetal heartbeat detected



With development of hypertension early in pregnancy (i.e. <20 wk), think gestational trophoblastic disease

### Partial (or Incomplete) Mole
- focal trophoblastic hyperplasia and hydropic villi are associated with fetus or fetal parts
- often triploid (XXY, XYY, XXX) with chromosome complement from both parents
  - usually related to single ovum fertilized by two sperm
- low risk of progression to malignant sequelae (<4%)
- associated with fetus, which may be growth-restricted, and/or have multiple congenital malformations
- clinical features
  - typically present similar to threatened/spontaneous/missed abortion
  - pathological diagnosis often made after D&C

### Investigations
- quantitative β-hCG levels (tumour marker) abnormally high for gestational age
- U/S findings
  - if complete: no fetus (classic "snow storm" due to swelling of villi)
  - if partial: molar degeneration of placenta ± fetal anomalies, multiple echogenic regions corresponding to hydropic villi, and focal intrauterine hemorrhage
- CXR (may show metastatic lesions)
- features of molar pregnancies at high risk of developing persistent GTN post-evacuation
  - local uterine invasion as high as 31%
  - β-hCG >100,000 IU/L
  - excessive uterine size
  - prominent theca-lutein cysts

### Treatment
- suction D&C with sharp curettage and oxytocin
- Rhogam® if Rh negative
- prophylactic chemotherapy of no proven benefit
- chemotherapy for GTN if develops after evacuation

### Follow-up
- contraception required to avoid pregnancy during entire follow-up period
- serial β-hCGs (as tumour marker) every week until negative x 3 (usually takes several wk), then monthly for 6-12 mo prior to trying to conceive again
- increase or plateau of β-hCG indicates GTN: patient needs chemotherapy

## GTN (MALIGNANT GTD)

### Invasive Mole or Persistent GTN
- diagnosis made by rising or plateau in β-hCG, development of metastases following treatment of documented molar pregnancy
- histology: molar tissue from D&C
- metastases are rare (4%)

### Choriocarcinoma
- often present with symptoms from metastases
- highly anaplastic, highly vascular
- no chorionic villi, elements of syncytiotrophoblast and cytotrophoblast
- may follow molar pregnancy, abortion, ectopic, or normal pregnancy

### Placental-Site Trophoblastic Tumour
- rare aggressive form of GTN
- abnormal growth of intermediate trophoblastic cells
- low β-hCG, production of human placental lactogen (hPL), relatively insensitive to chemotherapy

## CLASSIFICATION of GTN
- non-metastatic
  - ~15% of patients after molar evacuation
  - may present with abnormal bleeding
  - all have rising or plateau of β-hCG
  - negative metastases on staging investigations
- metastatic
  - 4% of patients after treatment of complete molar pregnancy
  - metastasis more common with choriocarcinoma, which tends toward early vascular invasion and widespread dissemination
  - if signs or symptoms suggest hematogenous spread, do not biopsy (they bleed)
    - lungs (80%): cough, hemoptysis, CXR lesion(s)
    - vagina (30%): vaginal bleeding, "blue lesions" on speculum exam
    - pelvis (20%): rectal bleeding (if invades bowel), U/S lesion(s)
    - liver (10%): elevated LFTs, U/S or CT findings
    - brain (10%): headaches, dizziness, seizure (symptoms of space-occupying lesion), CT/MRI findings
  - highly vascular tumour, which is more likely to bleed and result in anemia
  - all have rising or plateau of β-hCG
  - classification of metastatic GTN
    - divided into good prognosis and bad prognosis
    - features of bad prognosis
      - long duration (>4 mo from antecedent pregnancy)
      - high pre-treatment β-hCG titre: >100,000 IU/24 h urine or >40,000 IU/L of blood
      - brain or liver metastases
      - prior chemotherapy
      - metastatic disease following term pregnancy
    - good prognosis characterized by the absence of each of these features



Lungs are the primary site for malignant GTN metastases; when pelvic exam and chest x-ray are negative, metastases are uncommon

### Investigations (for Staging)
- blood work: CBC, electrolytes, creatinine, β-hCG, TSH, LFTs
- imaging: CXR, U/S pelvis only
- if CXR shows lung metastasis then CT abdo/pelvis, MRI brain
- if suspect brain metastasis but CT brain negative, consider lumbar puncture for CSF β-hCG
- ratio of plasma β-hCG:CSF β-hCG <60 indicates metastases

**Table 31. FIGO Staging and Management of Malignant GTN**

| Stage | Findings | Management |
|---|---|---|
| I | Disease confined to uterine corpus | Single agent chemotherapy for low risk disease (WHO score ≤6)<br>1st line: pulsed actinomycin D (Act-D) IV q2wk<br>Alternatives: MTX-based regimen<br>20% of patients need to switch to alternate single-agent regimen due to failure of β-hCG to return to normal<br>Combination chemotherapy (EMA-CO: etoposide, MTX, ACT-D, cyclophosphamide, vincristine) if high risk (WHO score ≥7) or if resistant to single-agent chemotherapy<br>Can consider hysterectomy if fertility not desired or placental-site trophoblastic tumour |
| II | Metastatic disease to genital structures | As above |
| III | Metastatic disease to lungs with or without genital tract involvement | As above |
| IV | Distant metastatic sites including brain, liver, kidney, GI tract | Usually high risk (EMA-CO) with surgical resection of sites of disease<br>Persistence/resistance to chemotherapy<br>Consider radiation for brain mets |

**Table 32. WHO Prognostic Score for GTD (2011)**

| | Score | | | |
|---|---|---|---|---|
| **Prognostic Factor** | **0** | **1** | **2** | **4** |
| **Maternal Age** | >40 | 40 | | |
| **Antecedent Pregnancy** | Mole | Abortion | Term | |
| **Interval (End of Antecedent Pregnancy to Chemotherapy in Months)** | <4 | 4-6 | 7-13 | >13 |
| **HCG IU/1** | <103 | 103-104 | 104-105 | >105 |
| **Number of Metastases** | 0 | 1-4 | 5-8 | >8 |
| **Site of Metastases** | Lung | Spleen, kidney | GI tract | Brain, liver |
| **Largest Tumour Mass** | | 3-5 cm | >5 cm | |
| **Prior Chemotherapy** | | | Single drug | Two drug |

### Follow-up (for GTN)

- contraception for all stages to avoid pregnancy during entire follow-up period
- stage I, II, III
  - weekly β-hCG until 3 consecutive normal results
  - then monthly x 12 mo
- stage IV
  - weekly β-hCG until 3 consecutive normal results
  - then monthly x 24 mo

### GTN Diagnosis

- β-hCG plateau: <10% drop in β-hCG over four values in 3 wk (e.g. days 1, 7, 14, and 21) OR
- β-hCG rise >20% in any two values over two wk or longer (e.g. measure at days 1, 7, 14) OR
- β-hCG persistently elevated >6 mo OR
- metastases on work-up

# Common Medications

**Table 33. Common Medications**

| Drug Name (Brand Name) | Action | Dosing Schedule | Indications | Side Effects (S/E), Contraindications (C/I), Drug Interactions (D/I) |
|---|---|---|---|---|
| **acyclovir (Zovirax®)** | Antiviral; inhibits DNA synthesis and viral replication | **First Episode**: 400 mg PO tid x 7-10 d<br>**Recurrence**: 400 mg PO tid x 5 d | Genital herpes | **S/E**: headache, GI upset<br>**D/I**: zidovudine, probenecid |
| **bromocriptine (Parlodel®)** | Dopaminomimetic, agonist at D2R and antagonist at D1R; acts directly on anterior pituitary cells to inhibit synthesis and release of prolactin | **Initial**: 1.25-2.5 mg PO qhs with food<br>Then: increase by 2.5 mg every 2-7 d as needed until optimal therapeutic response<br>**Usual Range**: 1.5-15 mg OD<br><br>For IVF:<br>**Initial**: 1.25 mg/d PO between days 4-6 of follicular phase<br>**Then**: 2.5 mg/d until 3 d after onset menstruation | Galactorrhea + amenorrhea 2° to hyperprolactinemia<br>Prolactin-dependent menstrual disorders and infertility<br>Prolactin-secreting adenomas (microadenomas, prior to surgery of macroadenomas)<br>IVF | **S/E**: N/V, headache, postural hypotension, somnolence<br>**C/I**: uncontrolled HTN, pregnancy-induced HTN, CAD, breastfeeding<br>**D/I**: domperidone, macrolides, octreotide |
| **clomiphene citrate (Clomid®)** | Increases output of pituitary gonadotropins to induce ovulation | 50 mg OD x 5 d<br>Try 100 mg or 160 mg OD<br>If ineffective 3 courses: adequate trial | Patients with persistent ovulatory dysfunction (e.g. amenorrhea, PCOS) who desire pregnancy | **S/E**: Common: hot flashes, abdominal discomfort, exaggerated cyclic ovarian enlargement, accentuation of Mittelschmerz<br>Rare: ovarian hyperstimulation syndrome, multiple pregnancy, visual blurring, birth defects<br>**C/I**: pregnancy, liver disease, hormone-dependent tumours, ovarian cyst, undiagnosed vaginal bleeding |
| **clotrimazole (Canesten®)** | Antifungal; disrupt fungal cell membrane | **Tablet**: 100 mg/d intravaginally x 7 d or 200 mg/d x 3 d or 500 mg x 1 dose<br>**Cream** (1 or 2%): 1 applicator intravaginally qhs x 3-7 d<br>**Topical**: apply bid x 7 d | Vulvovaginal candidiasis | **S/E**: vulvar/vaginal burning |
| **danazol (Cyclomen® [CAN]) (Danocrine® [US])** | Synthetic steroid: inhibits pituitary gonadotropin output and ovarian steroid synthesis<br>Has mild androgenic properties | 200-800 mg in 2-3 divided doses<br>Use for 3-6 mo<br>Biannual hepatic U/S required if >6 mo use | Endometriosis<br>1° menorrhagia/DUB | **S/E**: weight gain, acne, mild hirsutism, hepatic dysfunction<br>**C/I**: pregnancy, undiagnosed vaginal bleeding, breastfeeding, severely impaired renal/hepatic/cardiac function, porphyria, genital neoplasia, thromboembolic disease<br>**D/I**: warfarin, carbamazepine, cyclosporine, tacrolimus, anti-hypertensives |

**Table 33. Common Medications** (continued)

| Drug Name (Brand Name) | Action | Dosing Schedule | Indications | Side Effects (S/E), Contraindications (C/I), Drug Interactions (D/I) |
|---|---|---|---|---|
| **doxycycline** | Tetracycline derivative; inhibit protein synthesis | 100 mg PO bid x ≥7 d | Chlamydia, gonococcal infection, syphilis | **S/E**: GI upset, hepatotoxicity<br>**C/I**: pregnancy, severe hepatic dysfunction<br>**D/I**: warfarin, digoxin |
| **fluconazole (Diflucan®)** | Antifungal; disrupt fungal cell membrane | 150 mg PO x 1 dose | Vulvovaginal candidiasis unresponsive to clotrimazole | **S/E**: headache, rash, N/V, abdominal pain, diarrhea<br>**D/I**: terfenadine, cisapride, astemizole, hydrochlorothiazide, phenytoin, warfarin, rifampin |
| **leuprolide (Lupron®)** | Synthetic GnRH analog; induces reversible hypoestrogenic state | 3.75 mg IM q1mo or 11.25 mg IM q3mo<br>Usually ≤6 mo, check bone density if >6 mo<br>Retreatment with Lupron® alone not recommended because of effects on bone density | Endometriosis<br>Leiomyomata<br>DUB<br>Precocious puberty | **S/E**: hot flashes, sweats, headache, vaginitis, reduction in bone density, acne, GI upset<br>**C/I**: pregnancy, undiagnosed vaginal bleeding, breastfeeding |
| **menotropin (Pergonal®)** | Human gonadotropin with FSH and LH effects; induce ovulation and stimulate ovarian follicle development | 75-150 U of FSH and LH IM OD x 7-12 d, then 10,000 U HCG 1 d after last dose | Infertility | **S/E**: bloating, irritation at injection site, abdominal/pelvic pain, headache, N/V, multiple pregnancy<br>**C/I**: primary ovarian failure, intracranial lesion (e.g. pituitary tumour), uncontrolled thyroid/adrenal dysfunction, ovarian cyst (not PCOS), pregnancy, undiagnosed uterine bleeding |
| **metronidazole (Flagyl®)** | Bactericidal; forms toxic metabolites which damage bacterial DNA | 2 g PO x 1 dose or 500 mg PO bid x 7 d | Bacterial vaginosis, trichomonas vaginitis | **S/E**: headache, dizziness, N/V, diarrhea, disulfiram-like reaction (flushing, tachycardia, N/V)<br>**C/I**: pregnancy (1st trimester)<br>**D/I**: cisapride, warfarin, cimetidine, lithium, alcohol, amiodarone, milk thistle, carbamazepine |
| **oxybutinin (Ditropan®)** | Anticholinergic; relaxes bladder smooth muscle, inhibits involuntary detrusor contraction | 5 or 10 mg/d PO<br>May increase doses by 5 mg weekly to a max of 30 mg/d | Overactive bladder (urge incontinence) | **S/E**: dry mouth/eyes, constipation, palpitations, urinary retention, dizziness, headache<br>**C/I**: glaucoma, GI ileus, severe colitis, obstructive uropathy, use with caution if impaired hepatic/renal function |
| **tolterodine (Detrol®)** | Anticholinergic | 1-2 mg PO bid | Overactive bladder (urge incontinence) | **S/E**: anaphylaxis, psychosis, tachycardia, dry mouth/eyes, headache, constipation, urinary retention, chest pain, abdominal pain<br>**C/I**: glaucoma, gastric/urinary retention, use with caution if impaired hepatic/renal function |
| **tranexamic acid (Cyklokapron®)** | Anti-fibrinolytic; reversibly inhibits plasminogen activation | 1-1.5 g tid-qid for first 4 d of cycle<br>Max 4 g/d<br>Ophthalmic check if used for several wk | Menorrhagia | **S/E**: N/V, diarrhea, dizziness, rare cases of thrombosis, abdominal pain, MSK pain<br>**C/I**: thromboembolic disease, acquired disturbances of colour vision, subarachnoid hemorrhage, age <15 yr |
| **ulipristal acetate (Fibristal®)** | Selective progesterone receptor modulator (SPRM) | 5 mg PO OD for max 3 mo; first tablet taken anytime during first 7 d of menstruation | Leiomyoma (pre-operative) | **S/E**: headache, hot flushes, constipation, vertigo, endometrial thickening<br>**C/I**: pregnancy, undiagnosed vaginal bleeding, any gynecological cancer |
| **urofollitropin (Metrodin®)** | FSH | 75 U/d SC x 7-12 d | Ovulation induction in PCOS | **S/E**: ovarian enlargement or cysts, edema and pain at injection site, arterial thromboembolism, fever, abdominal pain, headache, multiple pregnancy<br>**C/I**: primary ovarian failure, intracranial lesion (e.g. pituitary tumour), uncontrolled thyroid/adrenal dysfunction, ovarian cyst (not PCOS), pregnancy, abnormal uterine bleeding |
| **combined oral contraceptive pill (OCP)** | Ovulatory suppression by inhibiting LH and FSH<br>Decidualization of endometrium<br>Thickening of cervical mucus to prevent sperm penetration | | Contraception<br>Disorders of menstruation | See Table 8-12 |
| **intrauterine device (IUD)**<br>**copper IUD (Nova-T®)**<br>**progesterone-releasing IUD (Mirena®, Jaydess®)** | **Copper IUD**: mild foreign body reaction in endometrium, which is toxic to sperm and alters sperm motility<br>**Progesterone-releasing IUD**: decidualization of endometrium and thickening of cervical mucus, may suppress ovulation | Contraceptive effects last 3 yr (Jaydess®); up to 5 yr (Copper IUD, Mirena®) | Same as above | See Table 8-12 |

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Notes

# H Hematology

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# Acronyms

| | |
|---|---|
| AFib | atrial fibrillation |
| AFLP | acute fatty liver of pregnancy |
| AIHA | autoimmune hemolytic anemia |
| ALL | acute lymphoblastic leukemia |
| AML | acute myeloid leukemia |
| ANC | absolute neutrophil count |
| APC | activated protein C |
| APL | acute promyelocytic leukemia |
| APS | antiphospholipid antibody syndrome |
| aPTT | activated partial thromboplastin time |
| ARDS | acute respiratory syndrome |
| ATIII | antithrombin III |
| BM | bone marrow |
| CBC | complete blood count |
| CHF | congestive heart failure |
| CLL | chronic lymphocytic leukemia |
| CML | chronic myeloid leukemia |
| CRP | C-reactive protein |
| DAT | direct antiglobulin test |
| DIC | disseminated intravascular coagulation |
| EPO | erythropoietin |
| ESR | erythrocyte sedimentation rate |
| ET | essential thrombocythemia |
| FNA | fine needle aspiration |
| G6PD | glucose-6-phosphate dehydrogenase |
| G-CSF | granulocyte-colony stimulating factor |
| GSH | glutathione |
| HA | hemolytic anemia |
| Hb | hemoglobin |
| Hct | hematocrit |
| HCV | hepatitis C virus |
| HIT | heparin-induced thrombocytopenia |
| HMWK | high molecular weight kininogen |
| HUS | hemolytic uremic syndrome |
| IBD | inflammatory bowel disease |
| IMF | idiopathic myelofibrosis |
| IPC | intermittent pneumatic compression |
| IPSS | international prognostic scoring system |
| ITP | immune thrombocytopenic purpura |
| LFTs | liver function tests |
| LMWH | low molecular weight heparin |
| MAHA/TMA | microangiopathic hemolytic anemia/thrombotic microangiopathy |
| MCH | mean corpuscular Hb |
| MCHC | mean corpuscular Hb concentration |
| MCV | mean corpuscular volume |
| MDS | myelodysplastic syndromes |
| MF | myelofibrosis |
| MGUS | monoclonal gammopathy of unknown significance |
| MM | multiple myeloma |
| MPN | myeloproliferative neoplasm |
| MPV | mean platelet volume |
| MUGA | multi-gated acquisition |
| N/V | nausea/vomiting |
| NHL | non-Hodgkin lymphoma |
| PCC | prothrombin complex concentrates |
| Ph | Philadelphia chromosome |
| PK | prekallikrein |
| PMN | polymorphonuclear neutrophil |
| PNH | paroxysmal nocturnal hemoglobinuria |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| PUD | peptic ulcer disease |
| PV | polycythemia vera |
| RBC | red blood cell |
| RCMD | refractory cytopenia with multilineage dysplasia |
| RCMD-RS | refractory cytopenia with multilineage dysplasia and ringed sideroblasts |
| RDW | RBC distribution width |
| SPEP | serum protein electrophoresis |
| SCT | stem cell transplantation |
| sTfR | soluble transferrin receptor |
| TIBC | total iron binding capacity |
| TPO | thrombopoietin |
| TT | thrombin time |
| TTP | thrombotic thrombocytopenic purpura |
| UFH | unfractionated heparin |
| UPEP | urine protein electrophoresis |
| VTE | venous thromboembolism |
| vWD | von Willebrand disease |
| vWF | von Willebrand factor |
| WBC | white blood cell |
| WHO | World Health Organization |
| XRT | radiation therapy |

# Basics of Hematology

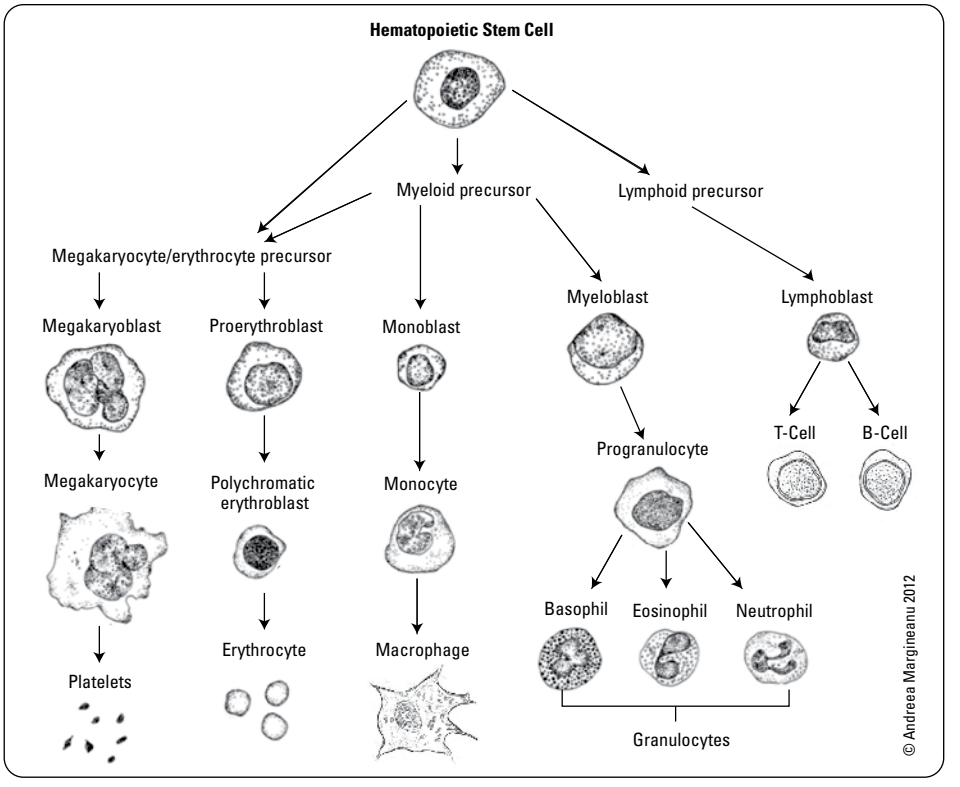



**Figure 1. Hematopoiesis**

**Erythrocyte:** carries oxygen from lungs to peripheral tissues

**Reticulocyte:** immature erythrocyte

**Neutrophil:** granulocyte integral in innate immunity; main cell in acute inflammation

**Eosinophil:** involved in response to parasites (especially helminths) and allergic response

**Basophil:** granulocyte mainly involved in allergy and parasitic infection

**Lymphocyte:** integral cell in adaptive immunity

**Monocyte:** involved in innate immunity; can differentiate into macrophage or dendritic cell

**Platelet:** mediator of primary hemostasis

**Plasma:** liquid component of blood containing water, proteins, coagulation factors, and immunoglobulins

**Serum:** equivalent to plasma minus clotting factors and fibrinogen

- over $10^{11}$ blood cells are produced daily
- sites of hematopoiesis in adults: pelvis, sternum, vertebral bodies, and cranium
- lifespan of mature cells in blood
  - erythrocytes (90-120 d), neutrophils (~1 d), platelets (7-10 d), lymphocytes (varies – memory cells persist for years)
- role of lymphoid organs
  - spleen: part of reticuloendothelial system, sequesters aged RBCs, removes opsonized cells, and site of antibody production
  - thymus: site of T-cell maturation and involutes with age
  - lymph nodes: sites of B and T-cell activation (adaptive immune response)

# Complete Blood Count

**Table 1. Common Terms Found in the CBC**

| Test | Definition | Normal Values* |
|---|---|---|
| **Red Blood Cell (RBC) Count** | The number of RBCs per volume of blood | 4.2-6.9 x $10^6$/mm$^3$ |
| **Hemoglobin (Hb)** | Amount of oxygen-carrying protein in the blood | 130-180 g/L (male)<br>120-160 g/L (female) |
| **Hematocrit (Hct)** | Percentage of a given volume of whole blood occupied by packed RBCs | 45%-62% (male)<br>37%-48% (female) |
| **Mean Corpuscular Volume (MCV)** | Measurement of RBC size | 80-100 μm$^3$ |
| **Mean Corpuscular Hb (MCH)** | Amount of oxygen-carrying Hb inside RBCs | 27-32 pg/cell |
| **Mean Corpuscular Hb Concentration (MCHC)** | Average concentration of Hb inside RBCs | 32%-36% |
| **RBC Distribution Width (RDW)** | Measurement of variance in RBC size | 11.0%-15.0% |
| **White Blood Cell (WBC) Count** | The number of WBCs per volume of blood | 4.3-10.8 x $10^9$/mm$^3$ |
| **WBC Differential** | Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils | 1.8-7.8 x $10^3$/mm$^3$<br>0.7-4.5 x $10^3$/mm$^3$<br>0.1-1.0 x $10^3$/mm$^3$<br>0.0-0.4 x $10^3$/mm$^3$<br>0.0-0.2 x $10^3$/mm$^3$ |
| **Platelet Count** | The number of platelets per volume of blood | 150-400 x $10^9$/mm$^3$ |
| **Mean Platelet Volume (MPV)** | Measurement of platelet size | 7.2-11.7 fL |
| **Reticulocytes** | Immature RBCs that contain no nucleus but have residual RNA | Normally make up 1% of total RBC count |

*Normal values may vary depending on site and age



To estimate Hb based on the Hct, multiply by 3.3



**Clinical Use of RDW**
To distinguish the etiologies of microcytosis:
- Iron deficiency: increased RDW (anisocytosis) as cells are of varying sizes in iron deficiency
- Thalassemia minor: normal RDW (also expect a high RBC count) as cells are of similar size due to genetic defect in Hb

### Approach to Interpreting a CBC

1. consider values in the context of individual's baseline:
   - up to 5% of population without disease may have values outside "normal" range
   - an individual may display a clinically significant change from their baseline without violating "normal" reference range
2. is one cell line affected or are several?
   - if all lines are low: pancytopenia (see *Pancytopenia*, H8)
   - if RBCs and platelets are low: consider a MAHA/TMA (see *Microangiopathic Hemolytic Anemia/Thrombotic Microangiopathy*, H22)
   - if single cell line affected: see *Common Presenting Problems*, H6

# Blood Film Interpretation

## RED BLOOD CELLS

### Size

- microcytic (MCV <80 μm$^3$), normocytic (MCV = 80-100 μm$^3$), macrocytic (MCV >100 μm$^3$)
- anisocytosis: RBCs with increased variability in size (increased RDW)
  - iron deficiency anemia, hemolytic anemias, myelofibrosis, blood transfusion, and MDS

### Colour

- hypochromic: increase in size of central pallor (normal = less than 1/3 of RBC diameter)
  - iron deficiency anemia, anemia of chronic disease, and sideroblastic anemia
- polychromasia: increased reticulocytes (pinkish-blue cells)
  - increased RBC production by bone marrow

### Shape

- poikilocytosis: increased proportion of RBCs of abnormal shape
  - iron deficiency anemia, myelofibrosis, severe $B_{12}$ deficiency, MDS, and burns

## Table 2. Common Erythrocyte Shapes

| Shape | Definition | Associated Conditions |
|---|---|---|
| **Discocyte**  | Biconcave disc | Normal RBC |
| **Spherocyte**  | Spherical RBC (due to loss of membrane) | Hereditary spherocytosis, immune hemolytic anemia |
| **Elliptocyte/Ovalcyte**  | Oval-shaped, elongated RBCs<br>• Elliptocytes: the RBC long axis is ≥2x the length of the short axis<br>• Ovalocytes: the RBC long axis is <2x the length of the short axis | Hereditary elliptocytosis, megaloblastic anemia, myelofibrosis, iron-deficiency, and MDS |
| **Schistocyte (helmet cell, fragment)**  | Fragmented cells (due to traumatic disruption of membrane) | Microangiopathic hemolytic anemia (HUS, aHUS, TTP, DIC, preeclampsia, HELLP, malignant HTN), vasculitis, glomerulonephritis, and prosthetic heart valve |
| **Sickle Cell**  | Sickle-shaped RBC (due to polymerization of hemoglobin S) | Sickle cell disorders: HbSC, HbSS |
| **Codocyte (target cell)**  | "Bull's eye" on dried film | Liver disease, hemoglobin SC, thalassemia, iron deficiency, and asplenia |
| **Dacrocyte (teardrop cell)**  | Single pointed end, looks like a teardrop | Myelofibrosis, MDS, thalassemia major, megaloblastic anemia, and bone marrow infiltration |
| **Acanthocyte (spur cell)**  | Distorted RBC with irregularly distributed thorn-like projections (due to abnormal membrane lipids) | Severe liver disease (spur cell anemia), starvation/anorexia, and post-splenectomy |
| **Echinocyte (burr cell)**  | RBC with numerous regularly spaced, small, spiny projections | Uremia, HUS, burns, cardiopulmonary bypass, post-transfusion, and storage artifact |
| **Rouleaux Formation**  | Aggregates of RBC resembling stacks of coins (due to increased plasma concentration of high molecular weight proteins) | Pregnancy is most common cause (due to physiological increase in fibrinogen)<br>Inflammatory conditions (due to polyclonal immunoglobulins)<br>Plasma cell dyscrasias (due to monoclonal paraproteinemia, e.g. multiple myeloma, macroglobulinemia)<br>Storage artifact |

DIC = disseminated intravascular coagulation; HELLP = hemolysis, elevated liver enzymes, and low platelet count; HUS = hemolytic uremic syndrome; aHUS = atypical HUS; TTP = thrombotic thrombocytopenic purpura
Illustrations: Ayalah Hutchins and Merry Shiyu Wang 2012

## Table 3. RBC Inclusions

| Inclusions | Definition | Associated Conditions |
|---|---|---|
| **Nucleus**  | Present in erythroblasts (immature RBCs) | Hyperplastic erythropoiesis (seen in hypoxia, hemolytic anemia), BM infiltration disorders, and MPNs (MF) |
| **Heinz Bodies**  | Denatured and precipitated hemoglobin | G6PD deficiency (post-exposure to oxidant), thalassemia, and unstable hemoglobins |
| **Howell-Jolly Bodies**  | Small nuclear remnant resembling a pyknotic nucleus | Post-splenectomy, hyposplenism (sickle cell disease), neonates, and megaloblastic anemia |
| **Basophilic Stippling**  | Deep blue granulations indicating ribosome aggregation | Thalassemia, heavy metal (Pb, Zn, Ag, Hg) poisoning, megaloblastic anemia, MDS, and hereditary (pyrimidine 5'nucleotidase deficiency) |
| **Sideroblasts**  | Late erythrocytes in BM with Fe containing granules in the cytoplasm | Hereditary, idiopathic, drugs, EtOH, hypothyroidism (see *Sideroblastic Anemia*, H16), and myelodysplastic syndrome, toxins (lead) |

BM = bone marrow; MF = myelofibrosis; MPN = myeloproliferative neoplasm
Illustrations: Ayalah Hutchins and Merry Shiyu Wang 2012

## WHITE BLOOD CELLS

- lymphocytes
  - comprise 30-40% of WBCs; great variation in "normal" lymphocyte morphology
- neutrophils
  - normally, only mature neutrophils (with 3-4 lobed nucleus) and band neutrophils (immediate precursor with horseshoe-shaped nucleus) are found in circulation
  - hypersegmented neutrophil: >5 lobes suggests megaloblastic process ($B_{12}$ or folate deficiency)
  - left shift (increased granulocyte precursors)
    - seen in leukemoid reactions: acute infections, pregnancy, neonates, hypoxia, shock, and myeloproliferative neoplasms (CML, MF)
- blasts
  - immature, undifferentiated precursors; associated with acute leukemia, MDS, and G-CSF (growth factor that stimulates neutrophil production) use

**Left Shift**
Refers to an increase in granulocyte precursors in the peripheral smear (myelocytes, metamyelocytes, promyelocytes, blasts). If present, implies increased marrow production of granulocytes (e.g. inflammation, infection, G-CSF administration, CML)
The presence of predominantly blasts in the peripheral smear without further differentiated precursor cells or mature neutrophils, suggests clonal cell disorder (MDS, acute leukemias)
If >20% of the total WBC differential consists of blasts, this is acute leukemia and is a medical emergency

**Table 4. Abnormal White Blood Cells on Film**

| Appearance | Definition | Associated Conditions |
|---|---|---|
| **Smudge Cell**  | Lymphocytes damaged during blood film preparation indicating cell fragility | CLL and other lymphoproliferative disorders |
| **Auer Rod**  | Cytoplasmic inclusions that form long needles in the cytoplasm of myeloblasts | Pathognomonic for acute myeloid leukemia (AML) |
| **Atypical Lymphocyte**  | Pale blue cytoplasm following RBC edges with pink granules | Viruses (particularly EBV) and T-cell large granular lymphocyte leukemia (T-LGL) |

EBV = Epstein-Barr virus; CLL = chronic lymphocytic leukemia
Illustrations: Ayalah Hutchins and Merry Shiyu Wang 2012 and Danielle Sayeau 2017

## PLATELETS

- small, purple, anuclear cell fragments

# Bone Marrow Aspiration and Biopsy

- sites: posterior iliac crest/spine, sternum (aspiration only)
- analyses: most often done together
  - aspiration: takes a fluid marrow sample for cellular morphology, flow cytometry, cytogenetics, molecular studies, and microbiology (C&S, acid-fast bacilli, and PCR)
    - note: differential diagnosis for a "dry tap": MF, hairy cell leukemia, bone marrow infiltration
  - biopsy: takes a sample of intact bone marrow to assess histology (architecture) and immunohistochemistry
  - only aspirates, not biopsies, can be obtained from the sternal site

### Indications

- unexplained CBC abnormalities
- diagnosis and evaluation of infiltrating cancers: plasma cell disorders, leukemias, and solid tumours
- diagnosis and staging of lymphoma or solid tumours
- evaluate iron metabolism and stores (gold standard, but rarely done)
- evaluate suspected deposition and storage disease (e.g. amyloidosis, Gaucher's disease)
- evaluate fever of unknown origin, suspected mycobacterial, fungal, and parasitic infections, or granulomatous disease
- evaluate unexplained splenomegaly
- confirm normal bone marrow in potential allogeneic hematopoietic cell donor

### Important Considerations

- consult a hematologist prior to conducting a bone marrow biopsy on a patient with an inherited (e.g. hemophilia, vWF disease) or acquired (e.g. DIC, anticoagulant therapy, coagulopathy of liver disease, and severe thrombocytopenia) bleeding diathesis to determine if pro-hemostatic therapy is indicated pre-procedure
- do not perform a bone marrow biopsy if there is evidence of infection over the targeted skin site

# Common Presenting Problems

## Anemia

### Definition

- a decrease in RBC mass that can be detected by hemoglobin (Hb) concentration, hematocrit (Hct), and RBC count
  - adult males: Hb <130 g/L or Hct <41%
  - adult females: Hb <120 g/L or Hct <36% (changes with pregnancy and trimester)

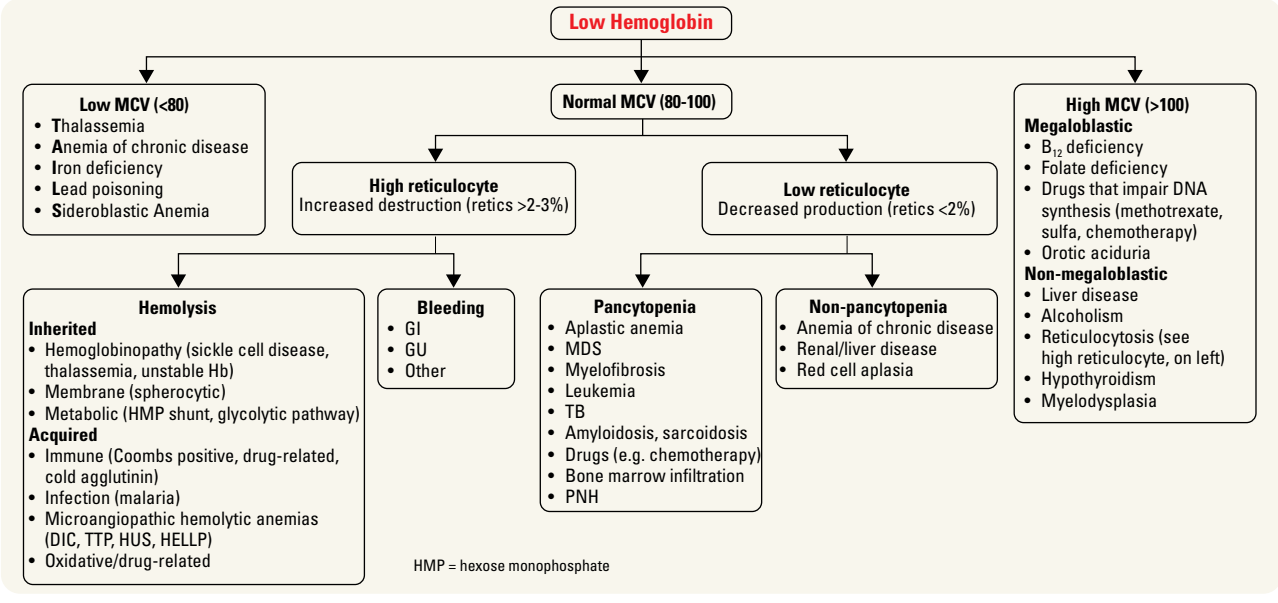



**Figure 2. Approach to anemia – classification by size of RBC**

### Clinical Features

- history
  - symptoms of anemia: fatigue, headache, light-headedness, malaise, weakness, decreased exercise tolerance, dyspnea, palpitations, dizziness, tinnitus, and syncope
  - acute vs. chronic, bleeding, systemic illness, diet (Fe, $B_{12}$ sources), alcohol, and family history
  - menstrual history: menorrhagia, menometrorrhagia
  - rule out pancytopenia (recurrent infection, mucosal bleeding, easy bruising)
- physical signs
  - HEENT: pallor in mucous membranes and conjunctiva at Hb <90 g/L (<9 g/dL), ocular bruits at Hb <55 g/L (<5.5 g/dL), angular cheilitis, jaundice
  - cardiac: tachycardia, orthostatic hypotension, systolic flow murmur, wide pulse pressure, signs of CHF
  - dermatologic: ecchymosis, petechiae, pallor in palmar skin creases at Hb <75 g/L, jaundice (if due to hemolysis), nail changes (spooning), and glossitis
  - splenomegaly, lymphadenopathy

**Reticulocytes**

- Reticulocytes are immature erythrocytes and are markers of erythrocyte production (↑ colour, ↓ central pallor, ↑ size)
- The reticulocyte count should always be interpreted in the context of Hb concentration
- Should normally increase when there is a decrease in RBC
- With blood loss, reticulocytes should increase 2-3x initially and then 5-7x over the next week
- A normal reticulocyte count in anemia should be interpreted as a sign of decreased production, and may result from BM infiltration, nutritional deficiency, or other causes

### Investigations

- rule out dilutional anemia (low Hb due to increased effective circulating volume)
- CBC with differential
- reticulocyte count and blood smear/film
- rule out nutritional deficit, gastrointestinal, and genitourinary disease in iron deficiency anemia
- additional laboratory investigations as indicated (see *Microcytic Anemia*, H13, *Normocytic Anemia*, H17, *Hemolytic Anemia*, H18, and *Macrocytic Anemia*, H23)
- N.B. may have a mixed picture with multiple concomitant nutritional deficiencies

## Erythrocytosis

### Definition

- an increase in the number of RBCs: Hb >185 g/L or Hct >52% (males); Hb >165 g/L or Hct >47% (females and African males)

### Etiology

- relative/spurious erythrocytosis (decreased plasma volume): diuretics, severe dehydration, burns, and "stress" (Gaisböck's syndrome)
- absolute erythrocytosis

**Table 5. Etiology of Erythrocytosis**

| Primary | Secondary | Inappropriate Production of Erythropoietin |
|---|---|---|
| **Polycythemia Vera (PV)** (see *Polycythemia Vera*, H42) | **Physiologic (poor tissue oxygenation/ hypoxia)**<br>Carbon monoxide poisoning<br>Heavy smoking<br>High altitude<br>**Pulmonary Disease**<br>COPD<br>Sleep apnea<br>Pulmonary hypertension<br>**Cardiovascular Disease**<br>R to L shunt (Eisenmenger syndrome)<br>RBC defects (Hb with increased $O_2$ affinity, methemoglobinemia) | **Tumours**<br>Hepatocellular carcinoma<br>Renal cell carcinoma<br>Cerebellar hemangioblastoma<br>Pheochromocytoma<br>Uterine leiomyoma<br>Ovarian tumour<br>**Other**<br>Polycystic kidney disease<br>Post-kidney transplant<br>Hydronephrosis<br>Androgens<br>Exogenous erythropoietin |

### Clinical Features
- secondary to high red cell mass and hyperviscosity
  - headache, dyspnea, dizziness, tinnitus, visual disturbances, hypertensive symptoms, and numbness/tingling
  - symptoms of angina, congestive heart failure, and aquagenic pruritus (only in MPNs)
- thrombosis (venous or arterial) or bleeding (seen with acquired vWD or acquired platelet dysfunction in MPNs)
- physical findings
  - splenomegaly ± hepatomegaly, facial plethora/ruddy complexion (70%) and/or palms, gout

### Investigations
- serum erythropoietin (EPO): differentiates primary (low/normal) from other etiologies (elevated)
  - search for tumour as source of EPO as indicated (e.g. abdominal U/S, CT head)
  - JAK-2 mutation analysis: positive in >96% of cases of PV
    - only send if low/normal EPO level
- ferritin (iron deficiency can mask the diagnosis; if iron deficient with reticulocytosis, suggestive of PV)

### Treatment
- if primary: see *Polycythemia Vera*, H42
- if secondary: treat underlying cause
  - $O_2$ for hypoxemia, CPAP for sleep apnea, surgery for EPO-secreting tumours
  - often cardiologists will be hesitant to treat high Hct in cyanotic patients

## Thrombocytopenia

### Definition
- platelet count <150 x $10^9$/L

### Clinical Features
- history: mucocutaneous bleeding (easy bruising, gingival bleeding), epistaxis, peri-operative bleeding (including dental procedures), heavy menstrual bleeding, and peripartum bleeding
- physical exam: bruising, petechiae, ecchymoses, non-palpable purpura, and wet purpura
- see *Disorders of Primary Hemostasis*, H27 for complications

### Investigations
- CBC and differential
- blood film
  - rule out factitious thrombocytopenia (platelet clumping or platelet satellitism)
  - decreased production: other cell line abnormalities, blasts (suggesting myeloid malignancy), hypersegmented PMNs (suggesting megaloblastic anemia), and leukoerythroblastic changes (suggesting BM infiltration or fibrosis)
  - increased destruction: large platelets (often seen in ITP), schistocytes (seen in MAHA/TMA)
- workup for nutritional deficiencies: $B_{12}$, RBC folate
- PT/INR, aPTT, and fibrinogen if DIC suspected
- LFT
- abdominal ultrasound to look for splenomegaly

### Treatments
- life threatening bleeding: platelet transfusion (repeat CBC 1 h post-transfusion to confirm an appropriate rise in counts)
- if secondary: treat underlying cause
- ITP: see *Immune Thrombocytopenic*, H27



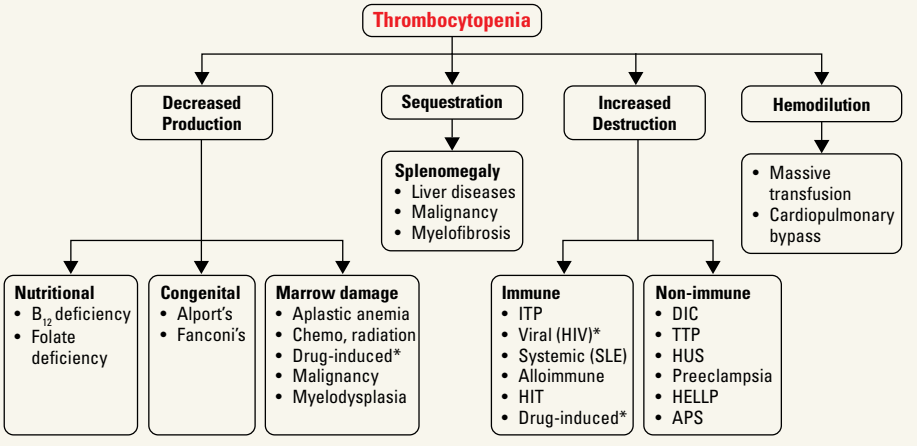
**Rule-of-thumb**: a deficit in all cell lines suggests decreased production, sequestration, or hemodilution. A deficit in platelets and RBCs suggests non-immune destruction or Evan's syndrome. An isolated thrombocytopenia suggests an immune-mediated process. In hospitalized patients, drugs and infection account for the majority of cases of thrombocytopenia



**Must rule out factitious thrombocytopenia:** platelet clumping secondary to EDTA antibodies present in serum. This can be seen on blood film and confirmed by repeating in a citrated sample (i.e. using a sodium citrate tube to collect blood, rather than EDTA)



**Wet vs. Dry Purpura**
Wet purpura: hemorrhaging of mucous membranes
Dry purpura: bruising or petechiae on skin surface




*In hospitalized patients most common causes of thrombocytopenia are drugs and infection

APS = antiphospholipid antibody syndrome; DIC = disseminated intravascular coagulation; HELLP = hemolysis, elevated liver enzymes, low platelet count; HIT = heparin induced thrombocytopenia; HUS = hemolytic uremic syndrome; ITP = idiopathic thrombocytopenic purpura; SLE =systemic lupus erythematosus; TTP = thrombotic thrombocytopenic purpura

**Figure 3. Approach to thrombocytopenia**
Adapted from: Cecil Essentials of Medicine

**References**
APS: see Hematology, H34
Aplastic Anemia: see Hematology, H17
$B_{12}$/Folate Deficiency: see Hematology, H24,H25
DIC: see Hematology, H32
HIT: see Hematology, H29
HIV: see Infectious Diseases, ID25
ITP: see Hematology, H27
Myelodysplasia: see Hematology, H39
Preeclampsia: see Obstetrics, OB24
SLE: see Rheumatology, RH11

# Thrombocytosis

## Definition
- platelet count >400 x $10^9$/L
- primary thrombocytosis (uncommon): due to myeloproliferative neoplasms (e.g. CML, polycythemia vera, primary myelofibrosis, and essential thrombocytosis; rarely associated with MDS)
- reactive/secondary thrombocytosis (common): acute phase reactant (e.g. surgery, inflammation, infection, trauma, bleeding, iron deficiency, neoplasms, and ischemic injury)

## Clinical Features
- history: trauma, surgery, splenectomy, infection, inflammation, bleeding, iron deficiency, prior diagnosis of chronic hematologic disorder, and constitutional symptoms (malignancy)
- vasomotor symptoms: headache, visual disturbances, lightheadedness, atypical chest pain, acral dysesthesia, erythromelalgia, livedo reticularis, and aquagenic pruritus
- clotting risk, bleeding risk (rare)
- physical exam: splenomegaly can be seen in myeloproliferative neoplasms (MPNs)

## Investigations
- CBC, peripheral blood film, serum ferritin concentration
- non-specific markers of infection or inflammation (e.g. CRP, ESR, ferritin)
- if reactive process has been ruled out, bone marrow biopsy may be required to rule out MPN/MDS

## Treatment
- primary: ASA ± cytoreductive agents (e.g. hydroxyurea, anagrelide, interferon-α)
- secondary: treat underlying cause

# Pancytopenia

## Definition
- a decrease in all hematopoietic cell lines

## Clinical Features
- anemia: fatigue (see *Anemia*, H6)
- leukopenia: recurrent infections (see *Neutropenia*, H9)
- thrombocytopenia: mucocutaneous bleeding (see *Thrombocytopenia*, H7)

## Investigations
- CBC, peripheral blood film, serum ferritin concentration, $B_{12}$, folate
- non-specific markers of infection or inflammation (e.g. CRP, ESR, ferritin)
- workup as per Figure 4 and presenting symptoms/physical exam
- if reactive process has been ruled out, bone marrow biopsy may be required

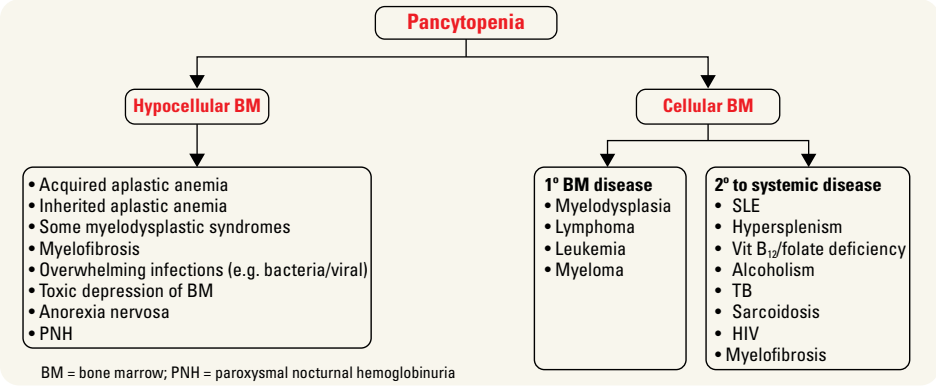



**Figure 4. Approach to pancytopenia**

# Neutrophilia

## Definition
- variable definition, but generally an absolute neutrophil count (ANC) >7.7 x $10^9$/L (WHO definition)

## Etiology
- primary neutrophilia
  - chronic myeloid leukemia (CML)
  - other myeloproliferative disorders: PV, ET, myelofibrosis
  - hereditary neutrophilia (autosomal dominant)
  - chronic idiopathic neutrophilia in otherwise healthy patients
  - leukocyte adhesion deficiency
- secondary neutrophilia
  - stress/exercise/epinephrine: movement of neutrophils from marginated pool into circulating pool
  - obesity
  - infection: leukocytosis with left shift ± toxic granulation, Döhle bodies (intra-cytoplasmic structures composed of agglutinated ribosomes)
  - inflammation: e.g. rheumatoid arthritis (RA), IBD, chronic hepatitis, MI, PE, and burns
  - malignancy: hematologic (i.e. marrow invasion by tumour) and non-hematologic (especially large cell lung cancer)
  - medications: glucocorticoids, β-agonists, lithium, G-CSF

## Clinical Features
- look for signs and symptoms of fever, inflammation, malignancy to determine appropriate further investigations
  - including lymphadenopathy and organomegaly
- examine oral cavity, teeth, peri-rectal area, genitals, and skin for signs of infection

## Investigations
- CBC and differential: mature neutrophils or bands >20% of total WBC suggests infection/inflammation
- blood film: Döhle bodies, toxic granulation, and cytoplasmic vacuoles in infection
- may require bone marrow biopsy if MPN suspected

## Treatment
- directed at underlying cause

# Neutropenia

## Definition
- mild: ANC 1.0-1.5 x $10^9$/L
- moderate: ANC 0.5-1.0 x $10^9$/L (risk of infection starts to increase)
- severe: ANC <0.5 x $10^9$/L
- profound: ANC <0.1 x $10^9$/L for >7 d



Absolute Neutrophil Count (ANC) = WBC count x (%PMNs + %bands)

Beware of fever + ANC <0.5 x $10^9$/L = FEBRILE NEUTROPENIA

### Etiology

**Table 6. Etiology of Neutropenia**

| Decreased Production | Peripheral Destruction/Sequestration | Excessive Margination (Transient Neutropenia) |
|---|---|---|
| **Infection**<br>Viral hepatitis, Epstein-Barr virus, HIV, TB, typhoid, malaria<br>**Hematological Diseases**<br>Idiopathic, aplastic anemia, myelofibrosis, BM infiltration, cyclic, PNH, MDS, immune-mediated<br>**Drug-Induced**<br>Alkylating agents, antimetabolites, anticonvulsants, antipsychotics, anti-inflammatory agents, anti-thyroid drugs<br>**Toxins/Chemicals**<br>High dose radiation, benzene, dichloro diphenyl trichloroethane (DDT)<br>**Nutritional Deficiency**<br>$B_{12}$, folate<br>**Idiopathic**<br>Constitutional neutropenia, benign cyclic neutropenia | Anti-neutrophil antibodies<br>Spleen or lung trapping<br>Autoimmune disorders: rheumatoid arthritis (Felty's syndrome), SLE<br>Granulomatosis with polyangiitis (formerly Wegener's)<br>Drugs: haptens (e.g. α-methyldopa) | Idiopathic (most common)<br>Overwhelming bacterial infection<br>Hemodialysis<br>Cardiopulmonary bypass<br>Racial variation (e.g. African or Ashkenazi Jewish descent) |

**Prophylactic Hematopoietic Colony-Stimulating Factors on Mortality and Infection**
Ann Intern Med 2007;147:400-411
**Purpose**: To review the effects of colony-stimulating factor (CSF) on mortality, infections, and febrile neutropenia in patients undergoing chemotherapy or stem-cell transplant (SCT).
**Study Selection**: 148 RCTs comparing the effects of CSFs to either placebo or no therapy were included. Prophylactic CSFs were given concurrently with or after initiation of chemotherapy.
**Results**: There were no differences in all-cause mortality or infection-related death between CSF and placebo groups. Compared to placebo or no therapy, CSFs reduced infection rate (median rate 38.9% vs. 43.1%; rate ratio 0.85), microbiologically documented infections (MR 23.5% vs. 28.6%; rate ratio 0.86), and febrile neutropenia (MR 25.3% vs. 44.2%; rate ratio 0.71).
**Conclusions**: Prophylactic CSFs decrease infection rates and episodes of febrile neutropenia in patients undergoing chemotherapy or SCT, but have no effect on mortality.

### Clinical Features
- fever, chills (only if infection present)
- infection by endogenous bacteria (e.g. *S. aureus*, Gram negatives from GI and GU tract)
- painful ulceration on skin, anus, mouth, and throat following colonization by opportunistic organisms
- avoid digital rectal exam

### Investigations
- dependent on degree of neutropenia, history, and symptoms
- ranges from observation with frequent CBCs to bone marrow aspiration and biopsy

### Treatment
- regular dental care: chronic gingivitis and recurrent stomatitis are major sources of morbidity
- treatment of febrile neutropenia
- in severe immune-mediated neutropenia, G-CSF may increase neutrophil counts
  - if no response to G-CSF, consider immunosuppression (e.g. steroids, cyclosporine, and methotrexate)

**G-CSF = Neupogen® = filgrastim**

## Lymphocytosis

### Definition
- absolute lymphocyte count >4.0 x $10^9$/L

### Etiology
- infection (reactive lymphocytosis)
  - viral infections (majority); particularly mononucleosis
  - TB, pertussis, brucellosis, toxoplasmosis
- smoking
- physiologic response to stress (e.g. trauma, status epilepticus)
- hypersensitivity (e.g. drugs, serum sickness)
- autoimmune (e.g. rheumatoid arthritis)
- neoplasm (e.g. CLL, B cell lymphocytosis of undetermined significance)

Presence of atypical lymphocytes suggests viral infection

Presence of smudge cells suggests a lymphoproliferative disorder if persistently elevated above 5.0 x $10^9$/L for >3 mo; consider flow cytometry of peripheral blood

### Investigations
- CBC, peripheral smear assessing lymphocyte morphology

### Treatment
- treat underlying cause

# Lymphopenia

### Definition
- absolute lymphocyte count <1.0 x $10^9$/L

### Etiology
- older age
- idiopathic CD4+ lymphocytopenia
- radiation
- HIV/AIDS, hepatitis B, hepatitis C
- malignancy/chemotherapeutic agents
- malnutrition, alcoholism
- autoimmune disease (e.g. SLE)

### Clinical Features
- opportunistic infections (see Infectious Diseases, ID32)

### Treatment
- treat underlying cause
- treat opportunistic infections aggressively and consider antimicrobial prophylaxis (see Infectious Diseases, ID28)

# Eosinophilia



**Basophilia and/or Eosinophilia**
Can be an indicator of CML or other myeloproliferative neoplasm, associated with pruritus due to excessive histamine production

### Definition
- absolute eosinophil count >0.5 x $10^9$/L

### Etiology
- primary: due to clonal bone marrow disorder
  - if no primary etiology identified, classified as hypereosinophilic syndrome
    - 6 mo of eosinophilia (count >1.5 x $10^9$/L) with no other detectable causes and end organ damage
    - can involve heart, bone marrow, and CNS
- secondary
  - most common causes are parasitic (usually helminth) infections and allergic reactions
  - less common causes
    - collagen vascular diseases (e.g. RA, polyarteritis nodosa, see Rheumatology, RH20)
    - respiratory causes (asthma, eosinophilic pneumonia, and Churg-Strauss)
    - cholesterol emboli
    - hematologic malignancy: see *Chronic Myeloid Leukemia*, H40 and *Hodgkin Lymphoma*, H45
    - adrenal insufficiency, see Endocrinology, E36
    - medications (penicillins)
    - atopic dermatitis

### Treatment
- treat underlying cause
- ensure strongyloides serology is collected to rule out infection before initiating steroids for patients at risk

# Agranulocytosis

### Definition
- absolute neutrophil count is <100/μL per microlitre

### Etiology
- associated with medications in 70% of cases: e.g. chemotherapy, clozapine, thionamides (antithyroid drugs), sulfasalazine, and ticlopidine
  - immune-mediated destruction of circulating granulocytes by drug-induced antibodies or direct toxic effects upon marrow granulocytic precursors

### Clinical Features
- abrupt onset of fever, chills, weakness, and oropharyngeal ulcers

### Prognosis
- high fatality without vigorous treatment

### Investigations/Treatment
- discontinue offending drug
- pan-culture and screen for infection if patient is febrile (blood cultures x2, urine culture, and chest x-ray as minimum, initiate broad-spectrum antibiotics)
- consider bone marrow aspirate and biopsy if cause unclear
- consider G-CSF

# Leukemoid Reaction

- blood findings resembling those seen in certain types of leukemia which reflect the response of healthy BM to cytokines released due to infection or trauma
- leukocytosis >50 x $10^9$/L, marked left shift (myelocytes, metamyelocytes, and bands in peripheral blood smear)

# Approach to Lymphadenopathy

## History

- constitutional/B-symptoms: seen in TB, lymphoma, other malignancies
- growth pattern: acute vs. chronic
- exposures: cats (cat scratch – *Bartonella henselae*), ticks (Lyme disease – *Borrelia burgdorferi*), and high risk behaviours (HIV)
- joint pain/swelling, rashes (connective tissue disorder)
- pruritus (seen in Hodgkin lymphoma)
- medications (can cause serum sickness → lymphadenopathy)

**Constitutional/B-Symptoms**
- Unexplained temperature >38°C
- Unexplained weight loss (>10% of body weight in 6 mo)
- Night sweats

## Clinical Features

- determine if lymphadenopathy is localized or generalized
- localized: typically reactive or neoplastic
  - cervical (bacterial/mycobacterial infections, ENT malignancies, and metastatic cancer)
  - supraclavicular
    - right (mediastinal, bronchogenic, esophageal cancer)
    - left (gastric, gall bladder, pancreas, renal, and testicular/ovarian cancer)
  - axillary (cat scratch fever, breast cancer, and metastatic cancer)
  - epitrochlear (infections, sarcoidosis, and lymphoma)
  - check for splenomegaly, constitutional symptoms

**Drugs that can cause Lymphadenopathy**
- Allopurinol
- Atenolol
- Captopril
- Carbamazepine
- Cephalosporins
- Gold
- Hydralazine
- Penicillin
- Phenytoin
- Primidone
- Pyrimethamine
- Quinidine
- Sulfonamides
- Sulindac

## Investigations

- CBC and differential, blood film
- if generalized, consider tuberculin test, HIV RNA, VDRL, Monospot®/EBV serology, ANA, and imaging
- if localized and no symptoms suggestive of malignancy, can observe 3-4 wk (if no resolution → biopsy)
- excisional biopsy is preferred as it preserves node architecture (essential for diagnosing lymphoma)
- in areas difficult to access (retroperitoneal, mediastinal/hilar) multiple core biopsies may be more practical/feasible
- FNA should NOT be used for diagnostic purposes in lymphoproliferative disease (excisional biopsy is the gold standard)
  - FNA is helpful for recurrence of solid tumour malignancy
  - imaging such as U/S or CT can provide more info, but generally adds little to diagnosis

**Table 7. Inflammatory vs. Neoplastic Lymph Nodes**

| Feature | Inflammatory | Neoplastic |
|---|---|---|
| Consistency | Fluctuant/soft | Firm/hard |
| Mobility | Mobile | Matted/immobile |
| Tenderness | Tender | Non-tender |
| Size | <2 cm | >2 cm |

*Note: these classifications are not absolute; lymphoma and CLL nodes can feel rubbery and are frequently mobile, non-tender

**Table 8. Differential Diagnosis of Generalized Lymphadenopathy**

| Reactive | Inflammatory | Neoplastic |
|---|---|---|
| Bacterial (TB, Lyme, brucellosis, cat scratch disease, and syphilis) | Collagen disease (RA, dermatomyositis, SLE, vasculitis, and Sjögren's) | Lymphoproliferative disorder/ lymphoma |
| Viral (EBV, CMV, HIV) | Drug hypersensitivity | Metastatic cancer |
| Parasitic (toxoplasmosis) | Sarcoidosis, amyloidosis | Histiocytosis X |
| Fungal (histoplasmosis) | Serum sickness | |

# Approach to Splenomegaly

**Table 9. Differential Diagnosis of Splenomegaly**

| Increased Demand for Splenic Function | | | Congestive | Infiltrative |
|---|---|---|---|---|
| **Hematological**<br>Nutritional anemias<br>Hemoglobinopathies<br>Hemolysis<br>Spherocytosis<br>Sequestration crisis<br>Elliptocytosis | **Infectious**<br>Viral e.g. EBV, HIV/AIDS, CMV<br>Bacterial e.g. Bacterial endocarditis, TB<br>Parasitic e.g. Malaria, Histoplasmosis, Leishmaniasis<br>Fungal | **Inflammatory**<br>SLE<br>Sarcoidosis<br>Felty syndrome<br>Still's disease | **Cirrhosis**<br>Portal HTN<br>Portal vein obstruction (including right heart failure)<br>Splenic vein thrombosis | **Non-Malignant**<br>Benign metaplasia<br>Cysts<br>Amyloidosis, Sarcoidosis<br>Hamartomas<br>Vascular abnormalities<br>Lysosomal storage diseases (Gaucher's, Niemann-Pick)<br>Glycogen storage diseases<br>**Malignant**<br>Leukemia (CML, CLL)<br>Lymphoproliferative disease<br>Hodgkin lymphoma<br>Myeloproliferative disorders<br>Metastatic tumour |

The underlined conditions cause *massive splenomegaly* (spleen crosses midline or reaches pelvis)

**Causes of Splenomegaly**

**CHINA**
**C**irrhosis/Congestion (portal HTN)
**H**ematological
**I**nfectious
**N**eoplasm (malignant, non-malignant)
**A**utoimmunue

### History
- constitutional symptoms, feeling of fullness in LUQ, and early satiety
- signs or symptoms of infection (e.g. mononucleosis) or malignancy
- history of liver disease, hemolytic anemia, or high-risk exposures

### Clinical Features
- jaundice, petechiae
- signs of chronic liver disease
- percussion (Castell's sign, Traube's space, and Nixon's method) and palpation
- associated lymphadenopathy or hepatomegaly
- signs of CHF

### Investigations
- CBC and differential, blood film
- as indicated: liver enzymes (AST, ALT, ALP, and GGT) and/or LFTs (platelet, INR, albumin, and bilirubin), reticulocyte count, Monospot®/EBV, haptoglobin, LDH, infectious, and autoimmune workup
- imaging
  - ultrasound of abdomen/liver to assess for cirrhosis and portal vein thrombosis (if positive, refer to hepatology)
  - echo for cardiac function
  - CT to rule out lymphoma and assess splenic lesions

# Microcytic Anemia

- MCV <80 fL
- see Figure 2, *Approach to Anemia*, H6

**Table 10. Iron Indices and Blood Film in Microcytic Anemia**

| | Lab Tests | | | | | Blood Film |
|---|---|---|---|---|---|---|
| | Ferritin | Serum Iron | TIBC | % saturation | RDW | |
| **Iron Deficiency Anemia** | ↓↓ | ↓ | ↑ | ↓ | ↑ (>15) | Hypochromic, microcytic |
| **Anemia of Chronic Disease** | N/↑ | ↓ | ↓ | N | N | Normocytic/microcytic |
| **Sideroblastic Anemia** | N/↑ | ↑ | N | N/↑ | ↑ | Dual population<br>Basophilic stippling |
| **Thalassemia** | N/↑ | N/↑ | N | N/↑ | N/↑ | Hypochromic, microcytic<br>Basophilic stippling<br>Poikilocytosis |

**Causes of Microcytic Anemia**

**TAILS**
**T**halassemia
**A**nemia of chronic disease
**I**ron deficiency
**L**ead poisoning
**S**ideroblastic anemia

# Iron Metabolism

### Iron Intake (Dietary)
- average North American adult diet = 10-20 mg iron (Fe) daily
- steady state absorption is 5-10% (0.5-2 mg/d); enhanced by citric acid, ascorbic acid (vitamin C) and reduced by polyphenols (e.g. in tea), phytate (e.g. in bran), dietary calcium, and soy protein
- males more likely to have positive Fe balance; up to 20% of menstruating females have negative Fe balance

## Iron Absorption and Transport

- dietary iron is absorbed in the duodenum (e.g. absorption impaired in IBD and Celiac disease)
- in circulation the majority of non-heme iron is bound to transferrin which transfers iron from enterocytes and storage pool sites (macrophages of the reticuloendothelial system and hepatocytes) to RBC precursors in the bone marrow

## Iron Levels

- hepcidin is a hormone produced by hepatocytes that regulates systemic iron levels
  - binds to iron exporter ferroportin (on duodenal enterocytes and reticuloendothelial cells) and induces its degradation, thereby inhibiting iron export into circulation (diminished absorption of iron and iron trapping in reticuloendothelial system cells)
  - hepcidin production is:
    - increased in states of iron overload (inhibiting additional iron absorption) and inflammation (mediating anemia of chronic inflammation through iron trapping)
    - decreased in states where erythropoiesis is increased (e.g. hemolysis) or oxygen tension is low

## Iron Storage

- ferritin
  - ferric iron ($Fe^{3+}$) complexed to a protein called apoferritin (liver, spleen, and bone marrow are main ferritin storage sites)
  - small quantities are present in plasma in equilibrium with intracellular ferritin
  - also an acute phase reactant – can be spuriously elevated despite low Fe stores in response to a stressor
- hemosiderin
  - aggregates or crystals of ferritin with the apoferritin partially removed
  - macrophage-monocyte system is main source of hemosiderin storage

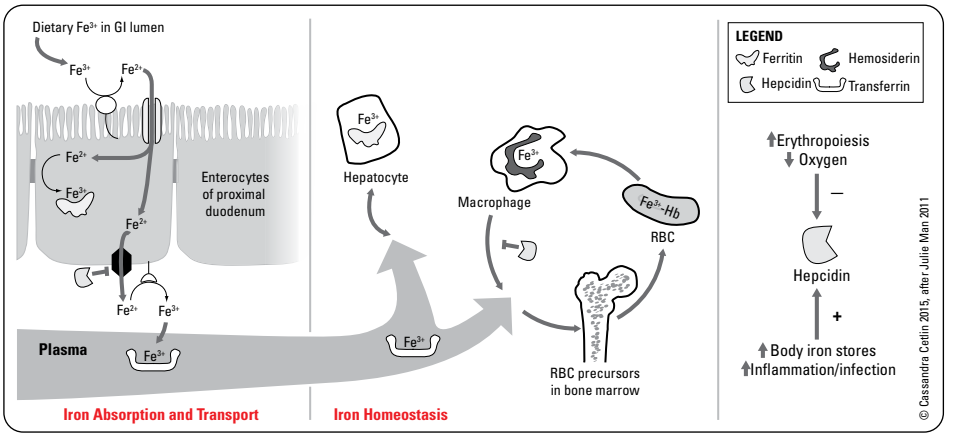



**Figure 5. Iron metabolism**

## Iron Indices

- bone marrow aspirate: gold standard test for assessment of iron stores (rarely done)
- serum ferritin: most important blood test for iron stores
  - decreased in iron deficiency anemia
  - elevated in infection, inflammation, malignancy, liver disease, hyperthyroidism, and iron overload
- serum iron: measure of all non-heme iron present in blood
  - varies significantly daily
- total iron binding capacity (TIBC): indirect measure of total amount of transferrin present in blood
  - normally, one third of TIBC is saturated with iron
  - increased TIBC has high specificity for decreased iron, low sensitivity
- saturation
  - serum Fe divided by TIBC, expressed as a proportion or a percentage
- soluble transferrin receptor (sTfR)
  - reflects the availability of iron at the tissue level
  - the transferrin receptor is expressed on the surface of erythroblasts and is responsible for iron uptake – some are cleaved off and are present in circulation as sTfR
  - in iron deficient states more transferrin receptors are expressed on erythroblasts leading to an increase in sTfR
  - low in reduced erythropoiesis and iron overload
  - useful in determining iron deficiency in the setting of chronic inflammatory disorders (see *Iron Deficiency Anemia,* H15)

# Iron Deficiency Anemia

- see Pediatrics, P43
- most common cause of anemia in North America

## Etiology

- increased demand
  - increased physiological need for iron in the body (e.g. pregnancy)
- decreased supply: dietary deficiencies (rarely the only etiology in the developed world)
  - cow's milk (infant diet), "tea and toast" diet (elderly), absorption imbalances, post-gastrectomy, malabsorption (IBD of duodenum, celiac disease, autoimmune atrophic gastritis, and *H.pylori* infection)
- increased losses
  - hemorrhage
    - obvious causes: menorrhagia, abnormal uterine bleeding, and frank GI bleed
    - occult: peptic ulcer disease, GI cancer
  - hemolysis
    - chronic intravascular hemolysis (e.g. PNH, cardiac valve RBC fragmentation)

## Clinical Features

- iron deficiency may cause fatigue before clinical anemia develops
- signs/symptoms of anemia: see *Anemia*, H6
- brittle hair, nail changes (brittle, koilonychia)
- pica (appetite for non-food substances e.g. ice, paint, and dirt)
- restless leg syndrome

**Plummer-Vinson Syndrome**
- Dysphagia (esophageal)
- Glossitis
- Iron deficiency anemia
- Stomatitis

## Investigations

- iron indices, including soluble transferrin receptor
  - low ferritin (<18 µg/L) is diagnostic of iron deficiency
  - ferritin is an acute phase reactant and is elevated in the setting of inflammatory conditions and liver disease; serum ferritin <100 µg/L in these settings is suggestive of iron deficiency, necessitating further workup
- peripheral blood film
  - hypochromic microcytosis: RBCs have low Hb levels due to lack of iron
  - pencil forms, anisocytosis
  - target cells
- bone marrow (gold standard but rarely done)
  - iron stain (Prussian blue) shows decreased iron in macrophages and in erythroid precursors (sideroblasts)
  - intermediate and late erythroblasts show micronormoblastic maturation

Iron deficiency anemia is a common presentation of chronic lower GI bleeds (right-sided colorectal cancer, angiodysplasia, etc.)

In males and in post-menopausal women, a GI workup is always warranted (gastroscopy, colonoscopy)

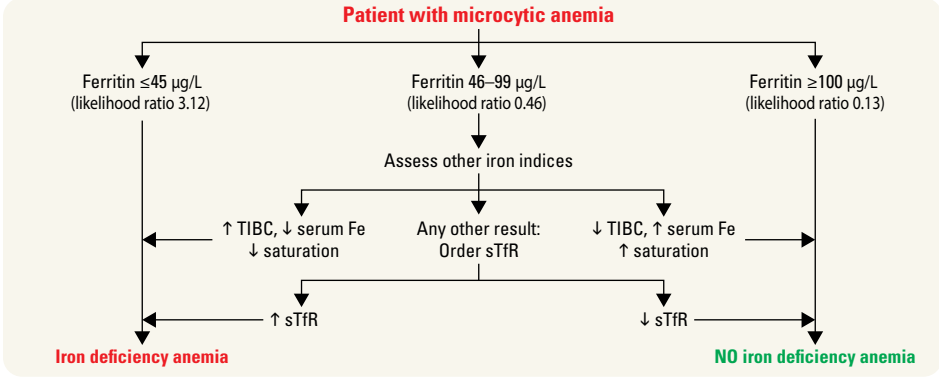



**Figure 6. Approach to interpreting iron indices**
Adapted from: Am Fam Physician 2007;75:671-678

## Treatment

- treat underlying cause
- supplementation
  - oral (capsules, syrup)
    - ferrous sulphate 325 mg OD (65 mg elemental iron), ferrous gluconate 300 mg OD (35 mg elemental iron), or ferrous fumarate 300 mg OD (100 mg elemental iron), polysaccharide iron complex (150 mg elemental iron), heme iron polypeptide (11 mg elemental iron)
    - supplement until anemia corrects, then continue for 3+ mo until serum ferritin returns to normal
    - recent studies demonstrate alternate day dosing may be superior to daily or more frequent dosing, due to improved absorption, though this is still an area of investigation
    - oral iron should be taken with citrus juice (vitamin C) to enhance absorption
  - IV (iron sucrose or dextran) can be considered if patient cannot tolerate or absorb oral iron
- monitoring response
  - reticulocyte count will begin to increase after one wk
  - Hb normalizes by 10 g/L per wk (if no blood loss)

# Anemia of Chronic Inflammation

### Etiology
- infection, malignancy, inflammatory, and rheumatologic disease
- chronic renal and liver disease
- endocrine disorders (e.g. DM, hypothyroidism, hypogonadism, and hypopituitarism)

### Pathophysiology
- an anemia of underproduction due to impaired iron utilization (hepcidin is a key regulatory peptide)
  - hepatic hepcidin production is increased in inflammatory processes, trapping iron in enterocytes and macrophages (via ferroportin inhibition), see Figure 5
  - reduced plasma iron levels make iron relatively unavailable for new hemoglobin synthesis
  - marrow unresponsive to normal or slightly elevated EPO
- mild hemolytic component is often present i.e. RBC survival is modestly decreased

### Investigations
- diagnosis of exclusion
- associated with elevation in acute phase reactants (ESR, CRP, fibrinogen, and platelets)
- peripheral blood
  - mild: usually normocytic and normochromic
  - moderate: may be microcytic and normochromic
  - severe: may be microcytic and hypochromic
  - absolute reticulocyte count is frequently low, reflecting overall decrease in RBC production
- "classic" serum iron indices
  - serum iron and TIBC low or normal, % saturation low
  - serum ferritin is normal or increased
- bone marrow
  - normal or increased iron stores
  - decreased or absent staining for iron in erythroid precursors

### Treatment
- treat underlying disease; only treat in patients who would benefit from a higher hemoglobin
- IV iron if no benefit from PO iron (overcomes sequestration in enterocytes)
- erythropoietin indicated in chronic renal failure; not to be used if patient has concomitant curative solid tumour malignancy; ensure Hb target <110 g/L

# Sideroblastic Anemia

- uncommon compared to iron deficiency anemia or anemia of chronic disease

### Sideroblasts
- erythrocytes with iron-containing (basophilic) granules in the cytoplasm
- "normal": granules are small and randomly spread in the cytoplasm
- "ring": iron deposits in mitochondria, forming large, abnormal granules that surround the nucleus
  - the hallmark of sideroblastic anemia

### Etiology
- due to defects in heme biosynthesis in erythroid precursors
- hereditary (rare): X-linked; median survival 10 yr
- idiopathic (acquired)
  - refractory anemia with ringed sideroblasts: a subtype of MDS (see *Myelodysplastic Syndromes*, H39)
  - may be a preleukemic phenomenon (1-2% transform to AML)
- reversible
  - drugs (isoniazid, chloramphenicol), alcohol, lead, copper deficiency, zinc toxicity, and hypothyroidism

### Clinical Features
- anemia symptoms (see *Anemia*, H6)
- hepatosplenomegaly, evidence of iron overload

### Investigations
- serum iron indices
  - increased serum $Fe^{2+}$, normal TIBC, increased ferritin, increased sTfR
- blood film/bone marrow biopsy
  - ringed sideroblasts (diagnostic hallmark)
  - RBCs are hypochromic; can be micro-, normo-, or macrocytic
  - anisocytosis, poikylocytosis, basophilic stippling

### Treatment
- depends on etiology
  - X-linked: high dose pyridoxine (vitamin $B_6$) in some cases
  - acquired: EPO and G-CSF
  - reversible: remove precipitating cause
- supportive transfusions for severe anemia

# Lead Poisoning

## Definition/Etiology
- blood lead levels greater than 80 µg/dL, possible symptomatology at 50 µg/dL
- identify source: consider occupational history, exposures history, and utensil history

## Clinical Features
- abdominal pain, constipation, irritability, and difficulty concentrating

## Treatment
- chelation therapy: dimercaprol and EDTA are first line agents

Consider lead poisoning in any child with microcytic anemia who lives in a house built before 1977

**Features of Lead Poisoning**

**LEAD**
**L**ead lines on gingivae and epiphyses of long bones on x-ray
**E**ncephalopathy and **E**rythrocyte basophilic stippling
**A**bdominal colic and microcytic **A**nemia (sideroblastic)
**D**rops (wrist and foot drop)

# Normocytic Anemia

- MCV 80-100 fL
- see Figure 2, *Approach to Anemia*, H6

# Aplastic Anemia

## Definition
- destruction of hematopoietic cells of the bone marrow leading to pancytopenia and hypocellular bone marrow

## Etiology

**Table 11. Etiology of Aplastic Anemia**

| Congenital | Acquired | |
|---|---|---|
| Fanconi's anemia<br>Shwachman-Diamond syndrome | **Idiopathic**<br>Often T-cell mediated<br>**Drugs**<br>Dose-related (i.e. chemotherapeutics)<br>Idiosyncratic (chloramphenicol, anti-malarials, and phenylbutazone)<br>**Toxins**<br>Benzene/organic solvents<br>DDT, insecticides | **Ionizing Radiation**<br>**Post-Viral Infection**<br>Parvovirus B19, EBV, HDV, HEV, HBV, HHV6, HIV<br>**Autoimmune** (rare)<br>SLE, Graft-versus-host disease<br>**Others**<br>PNH, pregnancy, anorexia nervosa, and thymoma |

**Causes of Normocytic Anemia**

**ABCD**
**A**cute blood loss
**B**one marrow failure
**C**hronic disease
**D**estruction (hemolysis)

## Clinical Features
- can present acutely or insidiously
- symptoms of anemia (see *Anemia*, H6), thrombocytopenia (see *Thrombocytopenia*, H7), and/or infection
- ± splenomegaly and lymphadenopathy (depending on the cause)

## Investigations
- exclude other causes of pancytopenia (see Figure 4), including PNH (50% of AA patients have PNH+ stem cell clones)
- CBC
  - anemia, neutropenia or thrombocytopenia (any combination) ± pancytopenia
  - decreased reticulocytes (<1% of the total RBC count)
- blood film
  - decreased number of normal RBCs
- bone marrow
  - aplasia or hypoplasia of marrow cells with fat replacement
  - decreased cellularity

## Treatment
- remove offending agents
- supportive care (red cell and platelet transfusions, antibiotics)
  - judicious use so as to not increase the risk of immune sensitization to blood products
  - iron chelation therapy for iron overload (build up of iron after multiple >20 units of blood transfusion)
- immunosuppressive therapy (for idiopathic aplastic anemia)
  - horse or rabbit anti-thymocyte globulin: 40-50% of patients respond
  - + cyclosporine (for improved response and survival)
- allogeneic bone marrow transplant
- growth factors: e.g. Eltrombopag (TPO receptor agonist), G-CSF, and EPO not effective

# Hemolytic Anemia

## Definition
- anemia due to a shortened survival of circulating RBCs, usually defined as <100 d
- uncommon cause for anemia (<5% of cases) with many etiologies (>200)

## Classification
- hereditary
  - abnormal membrane (spherocytosis, elliptocytosis)
  - abnormal enzymes (pyruvate kinase deficiency, G6PD deficiency)
  - abnormal hemoglobin synthesis (thalassemias, hemoglobinopathies)
- acquired
  - immune
    - autoimmune: warm vs. cold autoimmune hemolytic anemias (AIHA), see Table 14 *Classification of AIHA*, H22
    - alloimmune: hemolytic disease of the fetus/newborn and post-transfusion
  - non-immune
    - MAHA/TMA, now known as TMA: thrombus in blood vessel causes RBCs to be sheared – associated with DIC, HUS, aHUS, TTP, preeclampsia/HELLP, vasculitides, and malignant hypertension
    - other causes: PNH, hypersplenism, march hemoglobinuria (exertional hemolysis), infection (e.g. malaria), snake venoms, and mechanical heart valves
- also classified as intravascular or extravascular
  - intravascular: MAHA/TMA (e.g. TTP, DIC), infections (malaria, Clostridium), and PNH
  - extravascular: RBCs are coated with antibodies (AIHA) or have an abnormal membrane structure/ shape or inclusions

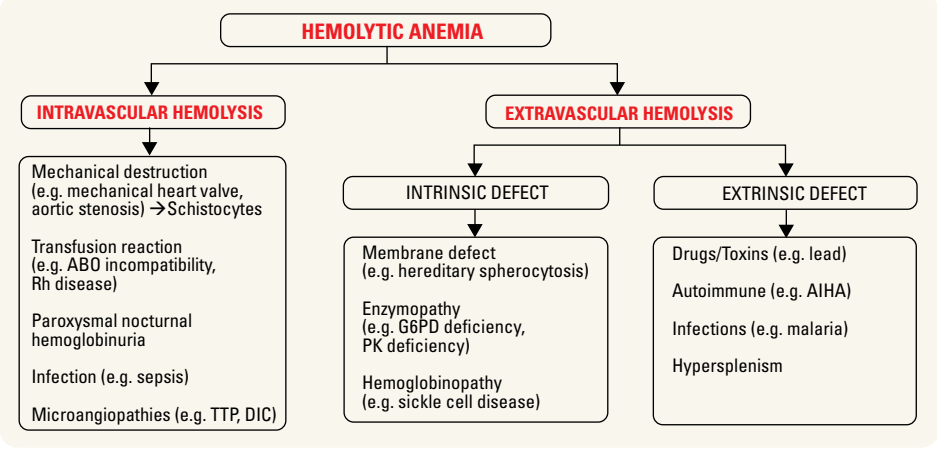



**Figure 7. Hemolytic anemia**

## Clinical Features Specific to HA
- jaundice
- dark urine (hemoglobinuria, bilirubin)
- cholelithiasis (pigment stones)
- potential for an aplastic crisis (i.e. BM suppression in overwhelming infection)
- iron overload with extravascular hemolysis
- iron deficiency with intravascular hemolysis

## Investigations

**Table 12. Investigations for Hemolytic Anemia**

| Screening Tests | Tests Specific For Intravascular Hemolysis |
|---|---|
| Increased LDH | Schistocytes on blood film |
| Decreased haptoglobin | Free hemoglobin in serum |
| Increased unconjugated bilirubin | Methemalbuminemia (heme + albumin) |
| Increased urobilinogen | Hemoglobinuria (immediate) |
| Reticulocytosis | Hemosiderinuria (delayed) – most sensitive |
| **Tests Specific for Extravascular Hemolysis** | |
| **Direct Antiglobulin Test (DAT) (direct Coombs)**<br>Detects IgG or complement on the surface of RBC<br>Add anti-IgG or anti-complement Ab to patient's RBCs; positive if agglutination<br>Indications: hemolytic disease of newborn, AIHA, hemolytic transfusion reaction<br>**Indirect Antiglobulin Test (indirect Coombs)**<br>Detects antibodies in serum that can recognize antigens on RBCs<br>Mix patient's serum + donor RBCs + Coombs serum (anti-human Ig Ab); positive if agglutination<br>Indications: cross-matching donor RBCs, atypical blood group, blood group Ab in pregnant women, AIHA | |

On blood film schistocytes reflect an intravascular hemolysis while spherocytes usually reflect an extravascular hemolysis

Disruption of the heme biosynthetic pathway causes the **porphyria** disorders

**Porphyrias**
Inherited or acquired disorder of defective heme synthesis leading to accumulation of porphyrin precursors. Typically present with non-specific clinical findings (abdominal pain, peripheral neuropathy, neuropsychiatric changes, and/or cutaneous photosensitivity)

**Heme Breakdown**

**Heme** → (Heme oxygenase) → **Biliverdin** → (Biliverdin reductase) → **Bilirubin**

**Laboratory Findings in HA**
- ↑ retics
- ↓ haptoglobin
- ↑ unconjugated bilirubin
- ↑ urobilinogen
- ↑ LDH

**Haptoglobin** is a circulating protein that mops up free hemoglobin, allowing its clearance in the spleen; when there is abundant free hemoglobin, haptoglobin is consumed, and levels decrease

**ThalasSEAmia**
β-Thal → prevalent in Mediterranean
α-Thal → prevalent in South East Asia (SEA) and Africa (α = Asia, Africa)

# Thalassemia

### Definition
- defects in production of the α or β chains of hemoglobin
  - resulting imbalance in globin chains leads to ineffective erythropoiesis and hemolysis in the spleen or BM
- clinical manifestations and treatment depend on specific gene and number of alleles affected
- common features
  - increasing severity with increasing number of alleles involved
  - hypochromic microcytic anemia
  - basophilic stippling, abnormally shaped RBCs on blood film

### Pathophysiology
- defect may be in any of the Hb genes
  - normally 4α genes in total; 2 on each copy of chromosome 16
  - normally 2β genes in total; 1 on each copy of chromosome 11
  - fetal hemoglobin, HbF (α2γ2), switches to adult forms HbA (α2β2) and HbA2 (α2δ2) at 3-6 mo of life
  - HbA constitutes 97% of adult hemoglobin
  - HbA2 constitutes 3% of adult hemoglobin

# β-Thalassemia Minor (Thalassemia Trait)

### Definition
- defect in single allele of β gene (heterozygous for one normal β globin allele and one β globin thalassemic allele)
- common in people of Mediterranean and Asian descent

### Clinical Features
- usually asymptomatic; a palpable spleen is very rare

### Investigations
- Hb (100-140 g/L), MCV (<70 fL), Fe (normal), RBC count (normal)
- peripheral blood film – microcytosis basophilic stippling
- Hb electrophoresis
  - specific: HbA2 increased to 3.5-5% (normal 1.5-3.5%)
  - non-specific: 50% have slight increase in HbF

### Treatment
- no treatment required
- genetic counselling for patient and family

**Microcytosis in β-Thal Minor**
Microcytosis is much more profound and the anemia is much milder than that of iron deficiency

# β-Thalassemia Major

### Definition
- defect in both alleles of β gene (homozygous, autosomal recessive)

### Pathophysiology
- ineffective chain synthesis leading to ineffective erythropoiesis, hemolysis of RBCs, and increase in HbF

### Clinical Features
- initial presentation at age 6-12 mo when HbA (α2/β2) normally replaces HbF (α2/γ2)
  - severe anemia, jaundice
- iron overload due to compensatory gastrointestinal iron uptake progressing to hemochromatosis
  - secondary to repeated transfusions and ineffective erythropoiesis
  - leads to iron-induced organ damage
- stunted growth and development (hypogonadal dwarf)
- gross hepatosplenomegaly (due to extramedullary hematopoiesis)
- radiologic changes (due to expanded marrow cavity) and extramedullary hematopoietic masses (erythroid tissue tumours)
  - skull x-ray has "hair-on-end" appearance
  - pathologic fractures common
- evidence of increased Hb catabolism (e.g. pigmented gallstones)
- death can result from:
  - untreated anemia (should transfuse)
  - infection (should identify and treat early)
  - iron overload (common): late complication from repeated transfusions and ineffective erythropoiesis

**Hemochromatosis Clinical Features**

**ABCDH**
**A**rthralgia
**B**ronze skin
**C**ardiomyopathy, cirrhosis of liver
**D**iabetes (pancreatic damage)
**H**ypogonadism (anterior pituitary damage)

### Investigations
- severe microcytic anemia (Hb <60 g/L)
- peripheral blood film: teardrop, target, hypochromatic, microcytic
- Hb electrophoresis
  - HbA: 0-10% (normal >95%)
  - HbA2 >2.5%
  - HbF: 90-100%

### Treatment
- lifelong regular transfusions to suppress endogenous erythropoiesis
- iron chelation (e.g. deferoxamine, deferasirox, and deferiprone) to prevent iron overload in organs and the formation of free radicals (which promote tissue damage and fibrosis)
- folic acid supplementation if not transfused
- allogeneic bone marrow transplantation (potentially curative) or cord blood transplant
- splenectomy (now performed less frequently)

## β-Thalassemia Intermedia

### Definition
- clinical diagnosis in patients whose clinical manifestations are too mild to be classified as thalassemia major, but too severe to be classified as thalassemia minor

### Clinical Features
- wide variety of clinical phenotypes
- in most cases of thalassemia intermedia, both β-globin genes affected
- three main mechanisms account for the milder phenotype compared to thalassemia major: (1) subnormal (vs. absent) β-chain synthesis, (2) increased number of γ chains, (3) coinheritance of α thalassemia (in some cases)
- complications more commonly seen in thalassemia intermedia than thalassemia major include extramedullary hematopoiesis, leg ulcers, gallstones, thrombosis, pulmonary hypertension, and growth retardation

### Treatment
- most patients only require periodic transfusions, although regular transfusions may eventually be necessary in adulthood (third to fourth decade of life)
- folic acid supplementation if not transfused
- due to ineffective erythropoiesis leading to downregulation of hepcidin, iron chelation therapy is required since iron overload develops even without frequent transfusion

## α-Thalassemia

### Definition
- defect(s) in α genes
- similar geographic distribution as β-thalassemia, but higher frequency among Asians and Africans

### Clinical Features
- 1 defective α gene (aa/a-): clinically silent; normal Hb, normal MCV
- 2 defective α genes (cis: aa/-- or trans: a-/a-): decreased MCV, normal Hb
  - N.B. cis 2-gene deletion more common in Asia vs. trans 2-gene deletion more common in Africa – this leads to increased risk of fetal hydrops in offspring of Asian patients vs. African patients
- 3 defective α genes (a-/--): HbH (β4) disease; presents in adults, decreased MCV, decreased Hb, and splenomegaly
- 4 defective α genes (--/--): Hb Barts (γ4) disease (hydrops fetalis); usually incompatible with life

### Investigations
- peripheral blood film – screen for HbH inclusion bodies with supravital stain
- electrophoresis can be used to identify HbH disease, but may miss 1- or 2-gene deletions; definitive diagnosis with DNA genotyping

### Treatment
- depends on degree of anemia, referral for genetic/prenatal counselling
  - 1 or 2 defective α genes: no treatment required
  - HbH disease: similar to β-thalassemia intermedia
  - HbBarts: no definitive treatment, majority of pregnancies terminated (fetal/maternal mortality risk), and intrauterine transfusion, stem cell transplants

## Sickle Cell Disease

### Definition
- autosomal recessive sickling disorders arise due to a mutant β-globin chain, most commonly caused by a Glu → Val substitution at position 6 (chromosome 11) resulting in HbS variant, rather than HbA (normal adult Hb)
  - increased incidence of HbS allele with Sub-Saharan African, Indian, Middle Eastern or Mediterranean heritage (thought to be protective against malaria)
- sickle cell disease occurs when an individual has two HbS genes (homozygous, HbSS) or one HbS gene + another mutant β-globin gene (compound heterozygote) – most commonly HbS-β-thal and HbSC disease

### Pathophysiology
- at low $pO_2$, deoxy HbS polymerizes leading to rigid crystal-like rods that distort membranes → 'sickles'
- the $pO_2$ level at which sickling occurs is related to the percentage of HbS present
- sickling aggravated by acidemia, increased $CO_2$, increased 2,3-DPG, fever, and osmolality

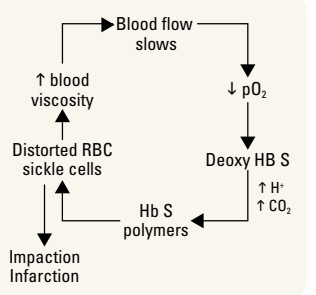



**Figure 8. Pathophysiology of sickling**

**Functional asplenism:** increased susceptibility to infection by encapsulated organisms
- *S. pneumoniae*
- *N. meningitidis*
- *H. influenza*
- *Salmonella* (osteomyelitis)

- fragile sickle cells then cause injury in two main ways
  1. fragile sickle cells hemolyze (nitric oxide depletion)
  2. occlusion of small vessels (hypoxia, ischemia-reperfusion injury)

## Clinical Features

- HbAS (sickle cell trait): patient will be asymptomatic except during extreme hypoxia or infection
  - increased risk of renal medullary carcinoma
- SCD-SS (HbSS)
  - chronic hemolytic anemia
  - jaundice in the first year of life
  - retarded growth and development ± skeletal changes
  - splenomegaly in childhood; splenic atrophy in adulthood
- SCD-SS often presents with acute pain episode
  1. aplastic crises
     - toxins and infections (especially parvovirus B19) transiently suppress bone marrow
  2. splenic sequestration crises
     - usually in children; significant pooling of blood in spleen resulting in acute Hb drop and shock
     - uncommon in adults due to asplenia from repeated infarction
  3. vaso-occlusive crises (infarction)
     - may affect various organs causing ischemia-reperfusion injury (especially in back, chest, abdomen, and extremities), fever, and leukocytosis
     - can cause a stroke or a silent myocardial infarction
     - precipitated by infections, dehydration, rapid change in temperature, pregnancy, menses, and alcohol
  4. acute chest syndrome
- SCD-SC (most common compound heterozygote)
  - 1:833 live births in African-Americans, common in West Africa
  - milder anemia than HbSS
  - similar complications as HbSS, although typically milder and less frequent (exception is proliferative sickle retinopathy, glomerulonephritis, and avascular necrosis)
  - spleen not always atrophic in adults

**Organs Affected by Vaso-Occlusive Crisis**

| Organ | Problem |
|---|---|
| **Brain** | Ischemic or hemorrhagic stroke, vasculopathy |
| **Eye** | Hemorrhage, blindness |
| **Liver** | Infarcts, RUQ syndrome |
| **Lung** | Acute chest syndrome, long-term pulmonary hypertension |
| **Gallbladder** | Stones |
| **Heart** | Hyperdynamic flow murmurs |
| **Spleen** | Enlarged (child); atrophic (adult) |
| **Kidney** | Hematuria, loss of renal concentrating ability, proteinuria |
| **Intestines** | Acute abdomen |
| **Placenta** | Stillbirths |
| **Penis** | Priapism |
| **Digits** | Dactylitis |
| **Femoral and Humeral Head** | Avascular necrosis |
| **Bone** | Infarction, infection |
| **Ankle** | Leg ulcers |

## Investigations

- sickle cell prep (detects sickling of RBCs under the microscope in response to $O_2$ lowering agent): determines the presence of a HbS allele, but does not distinguish HbAS from HbSS
- Hb electrophoresis distinguishes HbAS, HbSS, HbSC, and other variants
- all newborns in developed countries typically screened for SCD

**Table 13. Investigations for Sickle Cell Disease**

| | HbAS | HbSS |
|---|---|---|
| **CBC** | Normal | Increased reticulocytes, decreased Hb, decreased Hct |
| **Peripheral Blood** | Normal; possibly a few target cells | Sickled cells |
| **Hb Electrophoresis** | HbA fraction of 0.65 (65%)<br>HbS fraction of 0.35 (35%) | No HbA, only HbS and HbF (proportions change with age); normal amount of HbA2 |

## Treatment

- genetic counselling
- HbAS: no treatment required
- HbSC: treatment as per HbSS, but is dictated by symptom severity
- HbSS
  1. folic acid to prevent folate deficiency
  2. hydroxyurea to enhance production of HbF
     - mechanism of action: stops repression of Hb-γ chains and/or initiates differentiation of stem cells in which this gene is active
     - presence of HbF in the SS cells decreases polymerization and precipitation of HbS
     - N.B. hydroxyurea is cytotoxic and may cause bone marrow suppression
  3. treatment of vaso-occlusive crisis
     - supportive care: oxygen, hydration (reduces viscosity), correct acidosis, analgesics/opiates
     - indication for exchange transfusion: Hb <50-60 g/L, SCD complications (acute chest syndrome, aplastic crisis, hepatic or splenic sequestration, stroke), prevention of complications, pre-operative
     - less routinely: antimicrobials for suspected infection
  4. prevention of crises
     - establish diagnosis
     - avoid conditions that promote sickling (hypoxia, acidosis, dehydration, fever)
     - vaccination in childhood (pneumococcus, meningococcus, H. influenzae b)
     - prophylactic penicillin (age 3 mo-5 yr)
     - good hygiene, nutrition, and social support

**NIH Consensus Development Conference Statement: Hydroxyurea Treatment for Sickle Cell Disease**
*Ann Intern Med* 2008;148:932-938
**Efficacy**: Strong evidence for adolescents and adults and there is emerging data supporting its use in children. In the single RCT, the Hb level was higher in hydroxyurea recipients than placebo recipients after 2 yr (difference, 6 g/L), as was HbF (absolute difference, 3.2%). The median number of painful crises was 44% lower than in the placebo arm. The 12 observational studies that enrolled adults reported a relative increase in HbF of 4-20% and a relative reduction in crisis rates by 68-84%. Hospital admissions declined by 18-32%.
**Effectiveness**: Data is limited. It seems to be highly effective but is currently underutilized.
**Short-Term Harms (within 6 mo):** Dose-related leukopenia, thrombocytopenia, anemia, and decreased reticulocyte count. Others include decreased sperm production and dry skin.
**Long-Term Harms**: Birth defects in offspring of people receiving the drug, growth delays in children receiving the drug, and cancer in both children and adults who receive the drug.

5. screen for complications
   - regular blood work (CBC, reticulocytes, iron indices, BUN, LFTs, and creatinine)
   - urinalysis annually (proteinuria and glomerulopathy)
   - transcranial doppler annually until 16 yr old (stroke prevention)
   - retinal examinations annually from 8 yr old (screen for retinopathy)
   - echocardiography once in late childhood/early adulthood (screen for pulmonary hypertension)

# Autoimmune Hemolytic Anemia

**Table 14. Classification of AIHA**

| | Warm (75-90% cases) | Cold |
|---|---|---|
| **Antibody Allotype** | IgG | IgM |
| **Agglutination Temperature** | 37°C | 4-37°C |
| **Direct Coombs Test (direct anti-globulin test)** | Positive for IgG ± complement | Positive for complement |
| **Etiology** | Idiopathic<br>Secondary to lymphoproliferative disorder (e.g. CLL, Hodgkin lymphoma)<br>Secondary to autoimmune disease (e.g. SLE)<br>Drug-induced (e.g. penicillin, quinine, methyldopa) | Idiopathic<br>Secondary to infection (e.g. mycoplasma pneumonia, EBV)<br>Secondary to lymphoproliferative disorder (e.g. macroglobulinemia, CLL) |
| **Blood Film** | Spherocytes | Agglutination |
| **Management** | Treat underlying cause<br>Folic acid<br>Corticosteroids<br>Immunosuppression<br>Splenectomy<br>Rituximab (2nd-line to steroids) | Treat underlying cause<br>Folic acid<br>Warm patient/avoid cold<br>Rituximab regiments (1st-line)<br>Plasma exchange (2nd-line for high IgM levels)<br>Low dose alkylating agents (chlorambucil, cyclophosphamide) or interferon may be useful but less effective |

# Microangiopathic Hemolytic Anemia Thrombotic Microangiopathy

### Definition
- hemolytic anemia due to intravascular fragmentation of RBCs

### Etiology
- see *Thrombotic Thrombocytopenic Purpura* and *Hemolytic Uremic Syndrome*, H30
- see *Disseminated Intravascular Coagulation*, H32
- eclampsia, HELLP syndrome, AFLP
- malignant hypertension
- vasculitis
- malfunctioning heart valves
- metastatic carcinoma
- drugs (calcineurin inhibitors, quinine, simvastatin)
- infections (severe CMV or meningococcus)
- catastrophic antiphospholipid antibody syndrome

### Investigations
- blood film: evidence of hemolysis, schistocytes
- hemolytic workup (CBC, reticulocyte count, LDH, haptoglobin, indirect bilirubin)
- Coomb's test negative
- urine: hemosiderinuria, hemoglobinuria

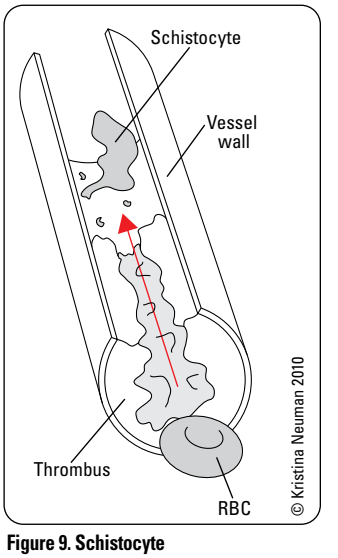


**Figure 9. Schistocyte**

# Hereditary Spherocytosis

- most common type of hereditary hemolytic anemia
- abnormality in RBC membrane proteins (e.g. spectrin)
  - spleen makes defective RBCs more spherocytic (and more fragile) by membrane removal; also acts as site of RBC destruction
- autosomal dominant with variable penetrance

### Investigations
- blood film (shows spherocytes), osmotic fragility (increased), molecular analysis for spectrin gene

### Treatment
- in severe cases, splenectomy and vaccination against pneumococcus, meningococcus, and *H. influenza* type b (avoid in early childhood)

# Hereditary Elliptocytosis

### Definition/Etiology
- abnormality in spectrin interaction with other membrane proteins
- autosomal dominant
- 25-75% elliptocytes
- hemolysis is usually mild

### Treatment
- immunizations; splenectomy for severe hemolysis

# Glucose-6-Phosphate Dehydrogenase Deficiency

### Definition
- deficiency in glucose-6-phosphate dehydrogenase (G6PD), corresponding to a lack of reduced glutathione (GSH) and leading to RBC sensitivity due to oxidative stress

### Pathophysiology
- X-linked recessive, prevalent in individuals of African, Asian, and Mediterranean descent

### Clinical Features
- frequently presents as episodic hemolysis precipitated by:
  - oxidative stress
  - drugs (e.g. sulfonamide, antimalarials, nitrofurantoin)
  - infection
  - food (fava beans)
- in neonates: can present as prolonged, pathologic neonatal jaundice

### Investigations
- neonatal screening
- G6PD assay (may not be useful if result is normal)
  - should not be done in acute crisis when reticulocyte count is high (reticulocytes have high G6PD levels)
- blood film
  - Heinz bodies (granules in RBCs due to oxidized Hb); passage through spleen results in the generation of bite cells
  - may have features of intravascular hemolysis (e.g. RBC fragments)

### Treatment
- folic acid
- stop offending drugs and avoid triggers
- transfusion in severe cases

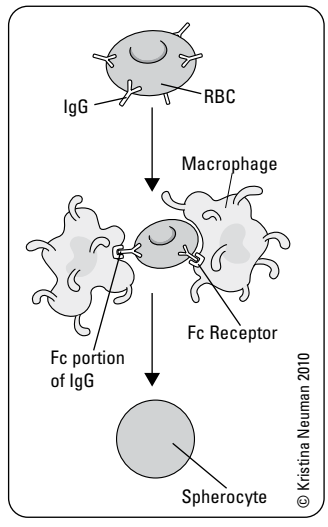



**Figure 10. Spherocytosis secondary to AIHA**

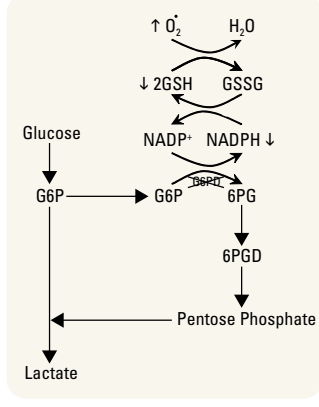



**Figure 11. G6PD deficiency**

# Macrocytic Anemia

- MCV >100 fL
- see Figure 2, *Approach to Anemia*, H6

**Table 15. Comparison Between Megaloblastic and Non-Megaloblastic Macrocytic Anemia**

| | Megaloblastic | Non-Megaloblastic |
|---|---|---|
| **Morphology** | Large, oval, nucleated RBC precursor<br>Hypersegmented neutrophils | Large round RBC<br>Normal neutrophils |
| **Pathophysiology** | Failure of DNA synthesis resulting in asynchronous maturation of RBC nucleus and cytoplasm | Reflects membrane abnormality with abnormal cholesterol metabolism |

**Causes of Macrocytic Anemia**

**ABCDEF**
**A**lcoholism (liver disease)
**B**$_{12}$ deficiency
**C**ompensatory reticulocytosis
**D**rugs (cytotoxic, AZT)/**D**ysplasia
**E**ndocrine (hypothyroidism)
**F**olate deficiency/**F**etus (pregnancy)

**Characteristics of Megaloblastic Macrocytic Anemia**
- Pancytopenia
- Hypersegmented neutrophils
- Megaloblastic bone marrow

# Vitamin $B_{12}$ Deficiency

- $B_{12}$ (cobalamin)
- binds to intrinsic factor (IF) secreted by gastric parietal cells
- absorbed in terminal ileum
- total body stores sufficient for 3-4 yr

## Etiology

**Table 16. Etiology of Vitamin $B_{12}$ Deficiency**

| Diet | Gastric | Intestinal Absorption | Genetic |
|---|---|---|---|
| **Strict vegan**<br>More likely to present in pediatric population<br>**Vegetarian in pregnancy**<br>**Malnutrition** | **Mucosal atrophy**<br>Gastritis, autoimmune<br>**Pernicious anemia** (see below)<br>**Post-gastrectomy** | **Malabsorption**<br>Crohn's, celiac sprue, pancreatic insufficiency, *H. pylori*<br>**Stagnant bowel**<br>Blind loop, stricture<br>**Fish tapeworm**<br>**Resection of ileum**<br>**Drugs**<br>Neomycin, biguanides, PPI, $N_2O$ anesthesia, metformin | **Transcobalamin II deficiency**<br>**IF receptor defect** |

## Pathophysiology of Pernicious Anemia

- auto-antibodies produced against gastric parietal cells leading to achlorhydria and lack of intrinsic factor secretion
- intrinsic factor is required to stabilize $B_{12}$ as it passes through the bowel
- decreased intrinsic factor leads to decreased ileal absorption of $B_{12}$
- may be associated with other autoimmune disorders (polyglandular endocrine insufficiency)
- most common in Northern European Caucasians, usually >30 yr old (median age of 60 yr old)

## Clinical Features

- neurological (severity of anemia and neurological sequelae depends on deficiency)
  - peripheral neuropathy (variable reversibility)
    - usually symmetrical, affecting lower limbs more than upper limbs
  - cord (irreversible damage)
    - subacute combined degeneration
      - posterior columns: decreased vibration sense, proprioception, 2-point discrimination, and paresthesia
      - pyramidal tracts: spastic weakness, ataxia
  - cerebral (common, reversible with $B_{12}$ therapy)
    - confusion, delirium, and dementia
  - cranial nerves (rare)
    - optic atrophy

## Investigations

- CBC, reticulocyte count
  - anemia often severe ± neutropenia ± thrombocytopenia
  - MCV >110 fL
  - low reticulocyte count relative to the degree of anemia (<2%)
- serum $B_{12}$ and RBC folate
  - caution: low serum $B_{12}$ leads to low RBC folate because of failure of folate polyglutamate synthesis in the absence of $B_{12}$
  - alternatively, can measure elevated urine metabolites (methylmalonate, homocysteine)
- blood film
  - oval macrocytes, hypersegmented neutrophils
- bone marrow
  - hypercellularity
  - nuclear-cytoplasmic asynchrony in RBC precursors (less mature nuclei than expected from the development of the cytoplasm)
- bilirubin and LDH
  - elevated unconjugated bilirubin and LDH due to breakdown of cells in BM
- Schilling test (radiolabeled $B_{12}$ test, rarely done) to distinguish pernicious anemia from other causes
  - anti-intrinsic factor antibody, anti-parietal cell antibody

## Treatment

- vitamin $B_{12}$ 1000 µg IM or 1000-1200 µg PO if intestinal absorption intact, route and duration depends on cause
- less frequent, higher doses may be as effective (e.g. 1000 µg IM q3mo)
- watch for hypokalemia and rebound thrombocytosis when treating severe megaloblastic anemia



**Oral Vitamin $B_{12}$ vs. Intramuscular Vitamin $B_{12}$ for Vitamin $B_{12}$ Deficiency**
Cochrane DB Syst Rev 2005;3:CD004655
**Study**: Systematic review. 2 RCTs met inclusion criteria; total 108 patients with follow-up from 90 d-4 mo.
**Intervention**: One study evaluated 1000 µg of oral $B_{12}$ compared to 1000 µg IM $B_{12}$ on the same dosing schedule. The other compared 2000 µg daily oral $B_{12}$ to 1000 µg IM $B_{12}$ on a less frequent dosing schedule. Neurological and hematological end points were evaluated.
**Results**: Meta-analysis was not attempted due to study heterogeneity. Both studies reported improvements in hematological and neurological end-points in both oral and IM groups. No significant difference was observed between groups in either study.
**Conclusions**: Limited data suggests high dose oral vitamin $B_{12}$ (1000-2000 µg) is equivalent to IM vitamin $B_{12}$ on the same or less frequent dosing schedule. This data is limited by small sample sizes and short follow-up periods. However, it suggests that a 3 to 4 mo trial of oral supplementation is a reasonable first choice for patients with $B_{12}$ deficiency.



**Schilling Test**

**Part 1**
- Tracer dose (1 µg) of radiolabeled $B_{12}$, given PO
- Flushing dose (1 mg) of unlabeled $B_{12}$ IM 1 h later to saturate tissue binders of $B_{12}$ thus allowing radioactive $B_{12}$ to be excreted in urine
- 24 h urine radiolabeled $B_{12}$ measured
- Normal >5% excretion (a normal excretion will only be seen if the low $B_{12}$ was due to dietary deficiency)

**Part 2**
- Same as part 1, but radiolabeled $B_{12}$ given with oral intrinsic factor
- Should be done only if first stage shows reduced excretion
- Normal test result (>5% excretion) = pernicious anemia
- Abnormal test result (<5% excretion) = intestinal causes (malabsorption)

# Folate Deficiency

- uncommon in developed countries due to extensive dietary supplementation (enriched in flour)
- folate stores are depleted in 3-6 mo
- folate commonly found in green, leafy vegetables and fortified cereals

### Etiology

**Table 17. Etiology of Folate Deficiency**

| Diet/Deficiency | Malabsorption | Drugs | Increased Demand |
|---|---|---|---|
| Alcoholism<br>Substance abuse<br>Elderly/infants<br>Poor intake | Celiac sprue<br>IBD<br>Infiltrative bowel disease<br>Short bowel syndrome | Anti-folates (methotrexate)<br>Anticonvulsants (phenytoin)<br>Alcohol<br>Oral contraceptive | Pregnancy<br>Hemolysis<br>Prematurity<br>Exfoliative dermatitis/psoriasis<br>Hemodialysis |

### Clinical Features
- anemia, mild jaundice, glossitis, diarrhea, confusion, pallor
- consider social history, alcohol/drug abuse, very poor diet (e.g. elderly, depressed)

### Investigations
- similar to $B_{12}$ deficiency (CBC, reticulocytes, blood film, RBC folate, and serum $B_{12}$)
- if decreased RBC folate, rule out $B_{12}$ deficiency as cause

### Management
- folic acid 1-5 mg PO OD x 1-4 mo; then 1 mg PO OD maintenance if cause is not reversible



Never give folate alone to an individual with megaloblastic anemia because it will mask $B_{12}$ deficiency and neurological degeneration will continue

# Hemostasis

## Stages of Hemostasis

### 1. Primary Hemostasis
- cellular defense – involves the platelet and vWF predominantly
- goal is rapid cessation of bleeding; main effect is on mucocutaneous bleeding
- vessel injury results in collagen/subendothelial matrix exposure and release of vasoconstrictors
- blood flow is impeded and platelets come into contact with damaged vessel wall (Figure 12a, H26)
  - activation: platelets are activated resulting in change of shape and release of adenosine diphosphate (ADP) and thromboxane A2
  - adhesion: platelets adhere to subendothelium via von Willebrand factor (vWF)
  - aggregation: these factors further recruit and aggregate more platelets resulting in formation of localized hemostatic plug

### 2. Secondary Hemostasis
- platelet plug is reinforced by production of fibrin clot (Figure 12b, H26)
- extrinsic (initiation) pathway: initiation of coagulation *in vivo*
- intrinsic (amplification) pathway: amplification once coagulation has started via positive feedback
- both intrinsic and extrinsic pathways converge onto the common pathway which results in thrombin generation and fibrin formation

### 3. Fibrin Stabilization
- conversion from soluble to insoluble and stable clot

### 4. Fibrinolysis
- once healing initiated, clot dissolution via action of the fibrinolytic system



**Phases of Hemostasis**

- **Primary hemostasis**
  Vascular response and platelet plug formation via vWF
- **Secondary hemostasis**
  Fibrin clot formation
- **Fibrin stabilization**
  Fibrinolysis



Check out this educational module created by St. Michael's Hospital residents and hematology faculty: www.coagtesting.com

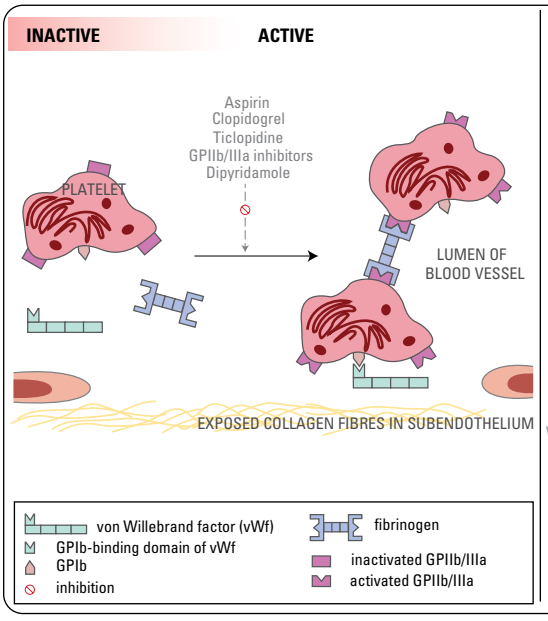



Figure 12a. Platelet activation cascade

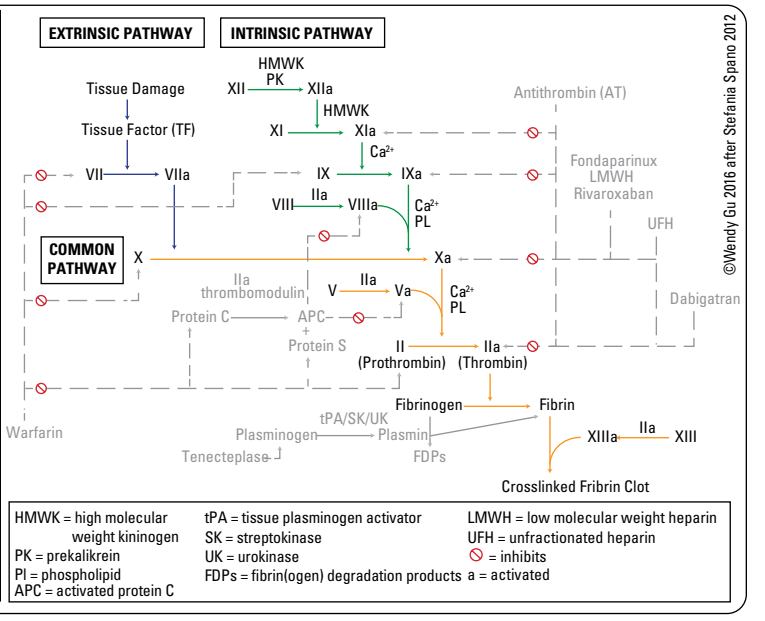



Figure 12b. Coagulation cascade

## Table 18. Commonly Used Tests of Hemostasis

| Type of Hemostasis | Test | Reference Range | Purpose | Examples of Associated Diagnoses |
|---|---|---|---|---|
| **Primary** | Platelet count | 150-400 x $10^9$/L | To quantitate platelet number | Low in ITP, HUS/TTP, DIC, HIT |
| **Secondary** | aPTT | 22-35 s | Measures intrinsic pathway (factors VIII, IX, XI, XII) and common pathway<br>Used to monitor heparin therapy | Prolonged in hemophilias A and B (if factor deficiency is below reagent threshold of detection)<br>N.B. Prolonged if lupus anti-coagulant present |
| | PT | 11-24 s | Measures extrinsic pathway (factor VII) and common pathway | Prolonged in vitamin K deficiency, vitamin K antagonist therapy (warfarin), factor VII deficiency |
| | INR | 0.9-1.2 | Used to monitor warfarin therapy and for assessment of hepatic function | |
| | Mixing studies | | May differentiate inhibitors of clotting factor(s) from a deficiency in clotting factors<br>Mix patient's plasma with normal plasma in 1:1 ratio and repeat abnormal test | Normalization of clotting time if deficiency of single clotting factor (normalization may not occur if multiple clotting factors are deficient)<br>Lack of normalization if inhibitor presence |
| **Fibrinolysis** | Euglobulin lysis time | N >90 min | Looks for accelerated fibrinolysis | May be accelerated in DIC or factor XIII deficiency<br>Decreased in hereditary deficiency of fibrinogen |
| **Other** | Fibrinogen<br>D-dimer<br>Specific factor assays (e.g. factor VIII)<br>Lupus anticoagulant<br>von Willebrand tests (vWF antigen, Ristocetin cofactor activity, factor VIII) | | | |

## Table 19. General Rules of Thumb: Signs and Symptoms of Disorders of Hemostasis

| | Primary (Platelet, vWF) | Secondary (Coagulation) |
|---|---|---|
| **Surface Cuts** | Excessive, prolonged bleeding | Normal/slightly prolonged bleeding |
| **Onset After Injury** | Immediate | Delayed |
| **Site of Bleeding** | Superficial i.e. mucosal (nasal, gingival, GI tract, vaginal), skin | Deep i.e. joints, muscles (excessive, post-traumatic) |
| **Lesions** | Petechiae, ecchymoses | Hemarthroses, hematomas |

**Tests of Secondary Hemostasis**

**PT**/INR: **T**ennis is played outside (Extrinsic pathway)
**PTT**: **T**able **T**ennis is played inside (Intrinsic pathway)

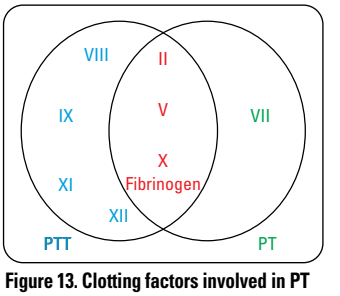



Figure 13. Clotting factors involved in PT and PTT

**Causes of an Prolonged PTT Without Bleeding include:**
1. Early contact factor (Factor XII, HMWK, PK) deficiency
2. Lupus anticoagulant
3. Inappropriate blood draw
4. Heparin contamination
5. Erythrocytosis (laboratory artifact)

**Consider PTT**
- IV heparin, argatroban monitoring
- Hemophilia A/B, factor XI deficiency, severe vWF

**Table 20. Lab Values in Disorders of Hemostasis**

| | PT | PTT | Platelet Count | Hemoglobin |
|---|---|---|---|---|
| **Hemophilia A/B** | N | ↑ | N | N* |
| **vWD** | N | ± | N/↓ | N* |
| **DIC** | ↑ | ↑ | ↓ | N/↓ |
| **Liver Failure** | ↑ | N/↑ | N/↓ | N |
| **ITP** | N | N | ↓ | N |
| **TTP** | N | N | ↓ | ↓ |

DIC = disseminated intravascular coagulation; ITP = idiopathic thrombocytopenic purpura; TTP = thrombotic thrombocytopenic purpura; vWD = von Willebrand disease;
* = anemia may develop from progressive iron deficiency and/or active bleeding

**Consider PT/INR**
- Warfarin
- Liver disease
- Risk factor for vitamin K deficiency (e.g. malabsorption, cholestasis, malnutrition)

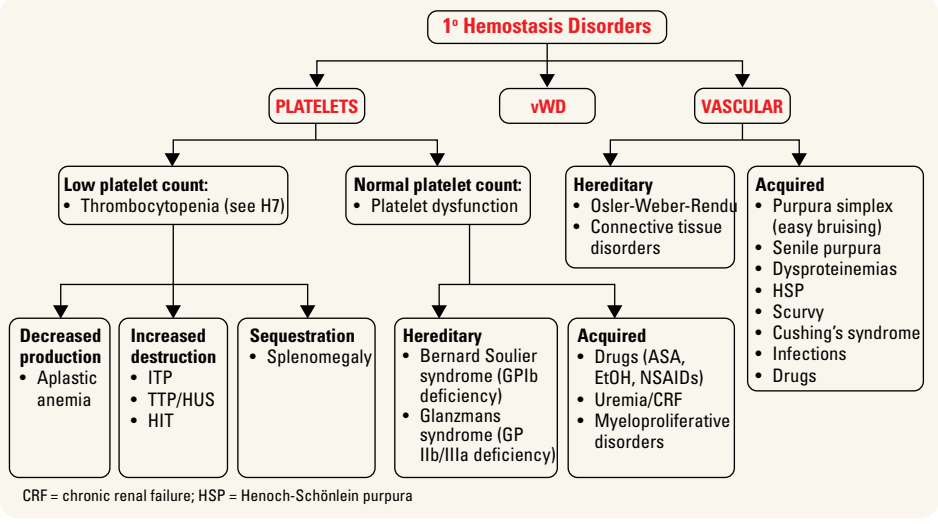
**Consider both PTT and PT/INR**
- Suspected DIC
- Trauma patient, or requiring massive transfusion protocol
- Bleeding patient
- Patient receiving thrombolytic therapy

# Disorders of Primary Hemostasis

## Definition

- inability to form an adequate platelet plug due to:
  - disorders of blood vessels
  - disorders of platelets: abnormal function/numbers
  - disorders of vWF

## Classification




CRF = chronic renal failure; HSP = Henoch-Schönlein purpura

**Figure 14. Approach to disorders of primary hemostasis**

**Drugs Associated with Thrombocytopenia**

| | | |
|---|---|---|
| TMP-SMX | Heparin | NSAIDs |
| Vancomycin | Digoxin | Acetaminophen |
| Rifampin | Amiodarone | Ethanol |
| Ethambutol | Quinidine | $H_2$-antagonists |
| Amphotericin B | Quinine (common) | Chemotherapy |

# Immune Thrombocytopenia

**Table 21. Features for Childhood vs. Adult Immune Thrombocytopenia**

| Features | Childhood ITP, see Pediatrics, P45 | Adult ITP |
|---|---|---|
| **Peak Age** | 2-6 yr | 20-40 yr |
| **Gender** | None | F>M (3:1) |
| **History of Recent Infection** | Common | Rare |
| **Onset of Bleed** | Abrupt | Insidious |
| **Duration** | Usually wk | Mo to yr |
| **Spontaneous Remissions** | 80% or more | Uncommon |

## Terminology of ITP

- also known as immune thrombocytopenia
- primary: isolated thrombocytopenia (platelet count <100 x $10^9$/L) with no other cause of thrombocytopenia
- secondary: thrombocytopenia associated with another condition (e.g. HIV, HCV, SLE, CLL)
- drug-induced: drug-dependent platelet antibodies causing platelet destruction

### Classification of Primary ITP
- acute: newly diagnosed (diagnosis to 3 mo)
- persistent: 3-12 mo from diagnosis
- chronic: >12 mo
- refractory: post-splenectomy

### Pathophysiology
- primary or secondary ITP
- an acquired immune-mediated disorder (pathophysiology incompletely understood)
  - anti-platelet antibodies bind to platelet surface → increased splenic clearance
  - impaired platelet production
  - helper T-cell and cytotoxic T-cell activation also implicated in platelet destruction

### Clinical Feature
- variable presentation: asymptomatic, fatigue, minimal bruising, mucocutaneous bleed (e.g. purpura, ecchymoses, petechiae, continuous epistaxis, menorrhagia), and intracranial bleed
- assess for symptoms/signs suggesting a secondary cause

### Investigations
- CBC and reticulocyte count: thrombocytopenia
- PT and aPTT: normal
- peripheral blood film: decreased platelets, giant platelets (rule out platelet clumping)
- HIV, HCV, *H. pylori* serology
- vitamin $B_{12}$, ANA, C3, C4, depending on clinical symptoms
- bone marrow aspirate and biopsy: increased number of megakaryocytes
  - recommended in patients >60 yr of age, pre-splenectomy or have failed traditional ITP therapy, those with systemic symptoms, an abnormal blood film
  - bone marrow aspirate and biopsy should be considered if there is any suspicion of diminished bone marrow function (e.g. myelodysplasia, infiltration)

### Treatment
- rarely indicated if platelets >30 x $10^9$/L unless active bleeding, trauma, or surgery
- emergency treatment (active bleeding [CNS, GI, or GU] or in need of emergency surgery)
  - general measures: stop drugs that reduce platelet function, control blood pressure, minimize trauma
  - corticosteroids: prednisone (1 mg/kg/d) or dexamethasone (40 mg PO/d x 4 d)
  - antifibrinolytic: tranexamic acid (1 g PO tid or 1 g IV q6h) if mucosal bleeding
  - IVIg 1 g/kg/d x 2 doses (raises platelet count faster than corticosteroids)
  - platelet transfusion: for refractory, major bleeding or need for urgent surgery (expect that platelet recovery will be diminished)
  - emergency splenectomy: may be considered, vaccinations prior if possible (pneumococcus, meningococcus, H. influenzae b)
  - management of intracranial bleeding: IV steroids, IVIg, platelets
- non-urgent treatment (platelet count <20-30 x $10^9$/L and no bleeding)
  - 1st-line
    - corticosteroids (dexamethasone 40 mg PO qd x 4 d x 1-4 cycles (not wk) or prednisone x 3 wk then slow taper)
    - IVIg
    - anti-D: appropriate for Rh+ non-splenectomized patients, but can cause hemolysis (avoid if low Hb at baseline or if DAT is positive)
  - 2nd-line
    - splenectomy (need vaccinations prior to splenectomy: pneumococcus, meningococcus, and *H. influenzae* b)
    - rituximab
  - 3rd-line
    - thrombopoietin (TPO) receptor agonists (romiplostim, eltrombopag) – may be considered for 2nd-line therapy if funding available
    - immunomodulating therapy (azathioprine, cyclophosphamide, danazol, and vincristine)

### Definitions of Response to Treatment
- complete response: platelet >100
- partial response: platelet 30-100
- no response: platelet <30

### Prognosis
- ~20% will not attain a hemostatic platelet count after first and second line therapy
- fluctuating course
- overall relatively benign, life-expectancy similar to general population (however, risk of mortality from bleeding/infection increases with advancing age)
- major concern is spontaneous intracranial hemorrhage if platelet <5 x $10^9$/L, more common in the elderly



**Mechanisms for HIV-associated Thrombocytopenia**
- Direct effect of HIV on marrow
- Immune-mediated platelet destruction
- Some anti-retrovirals reduce platelet production

## Table 22. Heparin-Induced Thrombocytopenia (HIT)

| | |
|---|---|
| **Pathophysiology** | Immune mediated<br>Ab recognizes a complex of heparin and platelet factor 4 (PF4) leading to platelet activation via platelet Fc receptor and activation of coagulation system |
| **Diagnosis** | Suspected with intermediate or high probability HIT Score<br>Confirm with ELISA testing and Serotonin Release Assay testing |
| **Onset of Decreased Platelets** | 5-15 d (if previously exposed to heparin within 100 d, HIT can develop in hours due to an anamnestic response) |
| **Risk of Thrombosis** | ~30% to 50% (25% of events are arterial) |
| **Clinical Features** | Bleeding complications uncommon<br>Venous thrombosis: DVT, PE, limb gangrene, cerebral sinus thrombosis<br>Arterial thrombosis: MI, stroke, acute limb ischemia, organ infarct (mesentery, kidney)<br>Heparin-induced skin necrosis (with LMWH)<br>Acute platelet activation syndromes: acute inflammatory reactions (e.g. fever/chills, flushing, etc.)<br>Transient global amnesia (rare) |
| **Specific Tests** | Pre-test clinical scoring models can help rule-out HIT: 4-Ts and the HIT Expert Probability (HEP) score<br>14C serotonin release assay (tests the functional ability of patient's plasma to activate platelets)<br>ELISA for HIT-Ig (more sensitive, less specific than serotonin assay, faster turnaround time, high negative predictive value)<br>Ultrasound of lower limb veins for DVT |
| **Management** | Clinical suspicion of HIT should prompt discontinuation of heparin and LMWH (specific tests take several days)<br>Initiate anticoagulation with a non-heparin anticoagulant:<br>e.g. argatroban, danaparoid, fondaparinux, bivalirudin unless there is a strong contraindication (duration of treatment at least 2-3 mo if no thrombotic event, and at least 3-6 mo if thrombotic event has occurred)<br>Warfarin should only be restarted when platelet count >150 x $10^9$/L<br>Allergy band and alert in patient records |

## Table 23. The 4-T Pre-Test Clinical Scoring Model for HIT

| Category | 2 Points | 1 Point | 0 Points |
|---|---|---|---|
| **1. Thrombocytopenia** | Platelet count fall >50%<br>AND<br>platelet nadir ≥20 x $10^9$/L | Platelet count fall 30-50%<br>OR<br>platelet nadir 10-19 x $10^9$/L | Platelet count fall <30%<br>OR<br>platelet nadir <10 x $10^9$/L |
| **2. Timing of Platelet Count Fall** | Clear onset between 5-10 d of heparin exposure<br>OR<br>platelet count fall at ≤1 d if prior heparin exposure within last 30 d | Consistent with fall in platelet count at 5-10 d but unclear (e.g. missing platelet counts)<br>OR<br>onset after day 10<br>OR<br>fall ≤1 d with prior heparin exposure within 30-100 d | Platelet count fall after <4 d of heparin exposure, and no recent heparin |
| **3. Thrombosis or Other Sequelae** | Confirmed new thrombosis, skin necrosis, or acute systemic reaction after IV unfractionated heparin bolus | Progressive or recurrent thrombosis, non-necrotizing (erythematous) skin lesions, or suspected thrombosis that has not been proven | None |
| **4. Other Causes for Thrombocytopenia** | None apparent | Possible | Definite |

6-8 points = high probability of HIT; 4-5 points = intermediate probability of HIT; 0-3 points = low probability of HIT
*J Thromb Haemos* 2006;4:759-765

**Heparin-Induced Thrombocytopenia**
- Heparin-induced thrombocytopenia (previously known as HIT type II): immune-mediated reaction following treatment with heparin leading to platelet and subsequent coagulation activation
- Heparin-associated thrombocytopenia (previously known as HIT type I): transient thrombocytopenia following administration of heparin

**Heparin-Associated Thrombocytopenia (previously known as HIT type I)**
- Direct heparin mediated platelet aggregation (non-immune)
- Platelets >100 X $10^9$/L
- Self-limited (no thrombotic risk)
- May continue with heparin therapy
- Onset 24-72 h

LMWH is also associated with HIT, but the risk is less than unfractionated heparin (2.6% in UFH vs. 0.2% in LMWH)

**American Society of Hematology Choosing Wisely Recommendation**
Don't test or treat for HIT in patients with low pre-test probability of HIT (4T's score of 0-3) as HIT can be excluded
Do not discontinue heparin or start a non-heparin anticoagulant in these low-risk patients because of increased risk of bleeding and increased cost of alternatives

# Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome

**Table 24. TTP and HUS**

| | TTP | HUS (see Pediatrics, P73) |
|---|---|---|
| **Epidemiology** | Predominantly adult | Predominantly children and elderly |
| **Etiology** | Deficiency of metalloproteinase that breaks down ultra-large vWF multimers: ADAMTS13<br>Congenital (genetic absence of ADAMTS-13)<br>Acquired (drugs, malignancy, transplant, and HIV-associated, idiopathic) | Shiga toxin (*E. coli* serotype O157:H7) in 90%<br>Other bacteria, viruses, genetic causes, and drugs |
| **Clinical Features** | 1. Thrombocytopenia<br>2. MAHA/TMA<br>3. Neurological symptoms: headache, confusion, focal defects, and seizures<br>4. Symptoms can be mild and non-specific | 1. Severe thrombocytopenia<br>2. MAHA/TMA<br>3. Acute kidney injury<br>4. Bloody Diarrhea<br>5. GI prodrome |
| **Investigations (both TTP, HUS)** | CBC and blood film: decreased platelets and increased schistocytes<br>PT, aPTT, fibrinogen: normal<br>Markers of hemolysis: increased unconjugated bilirubin, increased LDH, and decreased haptoglobin<br>Negative Coombs test<br>Creatinine and urea to follow renal function (TTP has nearly no kidney injury vs. HUS/drug mediated TTP which induces severe injury that is sudden in onset)<br>ADAMSTS-13 gene, activity or inhibitor testing (TTP) | |
| **Management** | Medical emergency<br>Plasma exchange ± steroids<br>Platelet transfusion avoided unless life-threatening bleed (associated with microvascular thrombosis)<br>Plasma infusion if plasmapheresis is not immediately available<br>*Caplacizumab in certain cases of acquired TTP<br>TTP mortality ~90% if untreated | Supportive therapy (fluids, RBC transfusion, nutrition, etc.)<br>Some evidence for plasma exchange<br>Possible role of Eculizumab (C5 antibody blocks complement activation) for neurologic symptoms |

Note: atypical HUS is a complex disease with different etiology, treatment depends on genetic abnormalities

**Pathophysiology of TTP**
- Large vWF multimers secreted by endothelial cells are typically rapidly cleaved by ADAMTS-13 protease
- Congenital TTP is due to a genetic deficiency in ADAMTS-13
- Acquired TTP (the more common form) antibodies against ADAMTS-13 are present

**Differential Diagnosis of TTP**
- DIC
- HUS
- aHUS
- HELLP
- Catastrophic antiphospholipid Ab syndrome
- Evans syndrome (AIHA + ITP)

# von Willebrand Disease

## Pathophysiology
- most common inherited bleeding disorder (prevalence of 1%)
- usually autosomal dominant (type 3 is autosomal recessive)
- women more commonly diagnosed (heavy menstrual bleeding, peripartum bleeding)
- qualitative defect or quantitative deficiency of vWF depending on type
  - vWF needed for platelet adhesion/aggregation and acts as chaperone for Factor VIII (extending its half-life in circulation), therefore abnormality of vWF can affect both primary and secondary hemostasis
  - vWF exists as a series of multimers ranging in size
    - largest multimers are most active in mediation of platelet adhesion/aggregation
    - both large and small multimers complex with Factor VIII
    - vWF levels vary according to blood group (non-group O patients have higher levels than group O patients)

## Classification
- type 1: mild quantitative defect (decreased amount of vWF and proportional decrease in vWF activity) – 80% of cases
- type 2: qualitative defect (vWF activity disproportionally lower than quantity) – 20% of cases
- type 3: severe total quantitative defect (virtually no vWF produced) – 1 per million

## Clinical Features
- bleeding history is the single most important predictor of an underlying bleeding disorder
- validated, standardized bleeding assessment tools (e.g. ISTH-BAT) to facilitate exploration of the bleeding history
- mucocutaneous bleeding (easy bruising, epistaxis (>10 min), heavy menstrual bleeding, peripartum bleeding, post-dental extraction bleeding, excessive post-operative bleeding, and unexplained gastrointestinal bleeding)
  - type 3 vWF patients can experience musculoskeletal bleeding due to significant deficiency in FVIII due to lack of FVIII chaperoning as vWF is absent
- family history of a bleeding disorder

## Investigations
- CBC, platelet, vWF:Antigen (determine how much vWF is present), vWF:Ristocetin cofactor activity (determine how well vWF binds to platelet), Factor VIII (determine how well vWF chaperones with FVIII), and PTT
- tests to further categorize type/subtype of vWD: multimer analysis, ristocetin induced platelet agglutination, and genetic studies

**Table 25. Investigations in vWD**

| Test | Expected Result | Test | Expected Result |
|---|---|---|---|
| PTT | N/↑ | von Willebrand antigen | ↓ |
| Factor VIII | N/↓ | Blood group | Affects antigen quantification (↓ in group O) |
| Plt Count | N/↓ | vWF multimer analysis | Multimer variants |
| Ristocetin Activity | ↓ (cofactor for vWF-Plt binding) | | |

### Treatment
- desmopressin (DDAVP®) is effective treatment for 85-90% of patients with type 1 vWD and for some subtypes of type 2 vWD
  - causes release of vWF and Factor VIII from endothelial cells
  - variable efficacy depending on disease type; tachyphylaxis occurs after 4 consecutive doses
  - need to document responsiveness with "DDAVP® challenge"
  - caution in children due to hyponatremia
- tranexamic acid (Cyklokapron®, antifibrinolytic) to stabilize clot formation
- vWF:FVIII concentrate (Humate P®, Wilate®) if DDAVP® unresponsive/clinically ineffective or for severe bleeding episode
  - need to monitor vWF and factor VIII levels (very high factor VIII level can be prothrombotic)
- gynecologic focused care for heavy menstrual bleeding (NB estrogens have the added benefit of increasing vWF levels)

### Prognosis
- patients with mild type 1 vWD have auto-correction of vWF deficiency in pregnancy
- most cases are mild-moderate, and only ~10% of cases require long-term prophylactic therapy



Consider vWD in all women with menorrhagia



vWD is the most common inheritable couagulation abnormality

# Disorders of Secondary Hemostasis

### Definition
- inability to form an adequate fibrin clot
  - disorders of clotting factors or co-factors
  - disorders of proteins associated with fibrinolysis
- characterized by delayed bleeding, deep muscular bleeding, and spontaneous hemarthroses

**Table 26. Classification of Secondary Hemostasis Disorders**

| Hereditary | Acquired |
|---|---|
| Factor VIII: Hemophilia A, vWD | Liver disease |
| Factor IX: Hemophilia B (Christmas Disease) | DIC |
| Factor XI | Vitamin K deficiency |
| Other factor deficiencies are rare | Acquired inhibitors (FVIII most common) |

## Hemophilia A (Factor VIII Deficiency)

### Pathophysiology
- X-linked recessive, 1/5000 males
- mild (>5% of normal factor level), moderate (1-5%), severe (<1%)

### Clinical Features
- see Table 19 – *Signs and Symptoms of Disorders of Hemostasis*, H26
- older patients may also acquired HIV or HCV from contaminated blood products

### Investigations
- prolonged aPTT, normal INR (PT)
- decreased Factor VIII (<40% of normal)

### Treatment
- desmopressin (DDAVP®) in mild hemophilia A
- Factor VIII concentrate for:
  - prophylaxis
  - on-demand (i.e. to treat a bleed)
- anti-fibrinolytic agents (e.g. tranexamic acid)

## Hemophilia B (Factor IX Deficiency)

- X-linked recessive, 1/30,000 males; approximately half have severe disease (factor IX activity <1% of normal)
- clinical and laboratory features identical to hemophilia A (except decreased Factor IX)
- treatment: Factor IX concentrate (prophylaxis or on-demand), anti-fibrinolytic agents

# Factor XI Deficiency

- autosomal recessive; more common in Ashkenazi Jewish population
- usually mild, often diagnosed in adulthood
- Factor XI level does not correlate with bleeding risk – risk of bleeding correlates with a previous history or family history of bleeding
- treatment: antifibrinolytic agents, frozen plasma, and Factor XI concentrate

# Liver Disease

- see Gastroenterology, G31

### Pathophysiology
- deficient synthesis of all factors except VIII (also made in endothelium)
- aberrant or diminished synthesis of fibrinogen (factor I)
- diminished synthesis of natural anticoagulants and altered regulation of fibrinolysis

### Investigations
- peripheral blood film: target cells
- primary hemostasis affected
  - thrombocytopenia 2º to hypersplenism, nutritional deficiency, direct bone marrow toxicity related to alcohol, diminished production from chronic viral infections (e.g. HCV), and decreased production of thrombopoietin
- secondary hemostasis affected
  - elevated INR (PT), aPTT, TT (thrombin time)
  - low fibrinogen in end-stage liver disease

**Investigations in Liver Disease**
Factor V, VII, VIII. Expect decreased V and VII because they have the shortest half-life. Factor VIII will be normal or increased because it is produced in the endothelium

### Treatment
- supportive, treat liver disease, blood products if active bleeding (frozen plasma, platelets, cryoprecipitate)

# Vitamin K Deficiency

### Etiology
- drugs
  - vitamin K antagonist (e.g. Warfarin) – diminished production of functional Factors II, VII, IX, X, proteins C and S
  - antibiotics eradicating gut flora, altering vitamin K uptake
- poor diet (especially in alcoholics) e.g. prolonged fasting or starvation
- biliary obstruction
- chronic liver disease (decreased stores)
- fat malabsorption (e.g. celiac disease, disorders of bile or pancreatic secretion, and intestinal disease, CF)
- hemorrhagic disease of newborn, see Pediatrics, P64

**Vitamin K Dependent Factors**
Vitamin K antagonists (e.g. warfarin) affect function of these factors:
"1972 Canada vs. Soviets"
X, IX, VII, II proteins C and S

### Investigations
- INR (PT) is elevated out of proportion to elevation of the aPTT
- decreased Factors II, VII, IX, X (vitamin K-dependent)

PT should improve within 24 h of adequately dosed vitamin K repletion (onset is in 6-12 h); if not, search for other causes

### Treatment
- hold anticoagulant if vitamin K antagonist on board
- vitamin K PO if no active bleeding
- if bleeding, give vitamin K 10 mg IV (reversal may take up to 12 h)
- if life-threatening bleeding and vitamin K antagonist used, give prothrombin complex concentrate (PCC) or FP if PCC contraindicated
  - PCCs are contraindicated in liver disease and if there is a previous history of HIT (PCC product contains heparin)

**American Society of Hematology Choosing Wisely Recommendation**
Do not administer plasma or prothrombin complex concentrates for non-emergent reversal of vitamin K antagonists (e.g. outside of the setting of major bleeding, intracranial hemorrhage, or anticipated emergent surgery)

# Disseminated Intravascular Coagulation

### Definition
- excessive, dysregulated release of plasmin and thrombin leading to intravascular coagulation and depletion of platelets, coagulation factors and fibrinogen
- risk of life-threatening hemorrhage or thromboembolism

### Etiology
- occurs as a complication of many other severe medical, surgical or obstetrical conditions
- widespread endothelial damage and extensive inflammatory cytokine release

DIC is a spectrum which may include thrombosis, bleeding, or both

**Factor Levels in Acquired Coagulopathies**

| Factor | Liver Disease | Vitamin K Def | DIC |
|---|---|---|---|
| V | ↓ | N | ↓ |
| VII | ↓ | ↓ | ↓ |
| VIII | N/↑ | N | ↓ |

**Table 27. Etiology of DIC**

| Activation of Procoagulant Activity | Endothelial Injury | Reticuloendothelial Injury | Vascular Stasis | Other |
|---|---|---|---|---|
| Antiphospholipid antibody syndrome (APS)<br>Intravascular hemolysis<br>Incompatible blood, malaria<br>Tissue injury<br>Obstetric complications, trauma, burns, crush injuries<br>Malignancy<br>Solid tumours, hematologic malignancies (especially APML)<br>Snake venom, fat embolism, heat stroke | Infections/sepsis<br>Vasculitis<br>Metastatic adenocarcinoma<br>Aortic aneurysm<br>Giant hemangioma | Liver disease<br>Splenectomy | Hypotension<br>Hypovolemia<br>Pulmonary embolus | Acute hypoxia/ acidosis (check lactate) |

**Important Etiologies of DIC**

**OMITS**
**O**bstetric complications
**M**alignancy
**I**nfection
**T**rauma
**S**hock

## Clinical Features

- presence of both hemorrhage and clotting

**Table 28. Clinical Features of DIC**

| Signs of Microvascular Thrombosis | Signs of Hemorrhagic Diathesis |
|---|---|
| **Neurological:** multifocal infarcts, delirium, coma, seizures<br>**Skin:** focal ischemia, superficial gangrene<br>**Renal:** oliguria, azotemia, cortical necrosis<br>**Pulmonary:** ARDS<br>**GI:** acute ulceration<br>**RBC:** microangiopathic hemolysis | Bleeding from any site in the body (2º to decreased platelets and clotting factors)<br>**Neurologic:** intracranial bleeding<br>**Skin:** petechiae, ecchymosis, oozing from puncture sites<br>**Renal:** hematuria<br>**Mucosal:** gingival oozing, epistaxis, massive bleeding |

**Clinical Prediction of DIC - International Society of Thrombosis and Hemostasis (ISTH) Calculator**

Presence of an underlying, predisposing condition is a requirement
Platelet count:
- 50-100 = 1 point
- <50 = 2 points

Fibrin-related marker (D-dimer or FDP):
- moderate increase = 2 points
- marked increase = 3 points

Fibrinogen (g/L):
- <1 = 1 point

PT:
- 3 - 6 s = 1 point
- >6 s = 2 points

DIC diagnosis is defined as ≥ 5 points

## Investigations

- primary hemostasis: decreased platelets
- secondary hemostasis: prolonged INR (PT), aPTT, TT, decreased fibrinogen and other factors
- fibrinolysis: increased FDPs or D-dimers and short euglobulin lysis time (i.e. accelerated fibrinolysis)
- extent of fibrin deposition: urine output and RBC fragmentation

## Treatment

- recognize early and treat underlying disorder – supportive measures: hemodynamic and/or ventilator support, aggressive hydration, and RBC transfusion if severe bleed
- in hemorrhage: replacement of hemostatic elements with platelet transfusion, frozen plasma, and cryoprecipitate
  - British Hematology Guidelines:
    - maintain platelets >50 x $10^9$/L, hemoglobin >80 g/L, calcium between 2.2-2.7 mmol/L, and avoid hypothermia
    - 4-5 units of FP if INR >1.5 or aPTT >38
    - 10 units of cryoprecipitate if fibrinogen <1 g/L
    - 1 adult dose of buffy-coat platelets if <10 x $10^9$/L (<20 if febrile, <50 before invasive procedure)
- in thrombotic phase: UFH or LMWH in critically ill, non-bleeding patients

**Table 29. Screening Test Abnormalities in Coagulopathies**

| Increased INR Only | Increased PTT Only | Both Increased |
|---|---|---|
| Warfarin<br>Vitamin K deficiency<br>Factor VII deficiency<br>Liver disease<br>Factor VII inhibitors | Hemophilia A and B<br>Heparin<br>Antiphospholipid Ab<br>Intrinsic factor inhibitors (e.g. FVIII)<br>Factor XI and XII deficiency | Prothrombin deficiency<br>Severe fibrinogen deficiency<br>Factor V and X deficiency<br>Severe liver disease<br>Factor V and X, prothrombin, and fibrinogen inhibitors<br>Excessive anticoagulation<br>Severe vitamin K deficiency |

**Differential Diagnosis of Elevated D-Dimer**

- Arterial thromboembolic disease (MI, cerebrovascular accident, acute limb ischemia, AFib, intracardiac thrombus)
- Venous thromboembolic disease (DVT, PE)
- DIC
- Preeclampsia and eclampsia
- Abnormal fibrinolysis; use of thrombolytic agents
- Cardiovascular disease, CHF
- Severe infection/sepsis/inflammation
- Surgery/trauma (tissue ischemia, necrosis)
- Systemic inflammatory response syndrome
- Vasoocclusive episode of sickle cell disease
- Severe liver disease
- Malignancy
- Renal disease (nephrotic syndrome, acute/chronic renal failure)
- Normal pregnancy
- Venous malformation

# Hypercoagulable Disorders

## Hypercoagulability Workup – Venous Thrombosis

- workup for hypercoagulable state is controversial and should only be done if it will alter treatment decisions
  - recommendations for a hypercoagulable workup include:
    - patients with recurrent or multiple thrombosis only if it will change management plans
    - warfarin-induced skin necrosis or neonatal purpura fulminans (protein C or S deficiency)
    - consider for patients with a family history of VTE who are considering OCP use
    - consider for patients who present with thrombosis at an unusual venous site only if it will change management plans
    - workup for malignancy is suggested in the event of abnormal blood work, constitutional symptoms or physical exam suggestive of cancer
  - arterial thrombotic events due to a hypercoagulable state are typically associated with APLA, HIT, JAK2 MPNs, and PNH, not hereditary thrombophilias

**American Society of Hematology Choosing Wisely Recommendations**

1. Do not test for thrombophilia in adult patients with venous thromboembolism occurring in the setting of major transient risk factors (surgery, trauma, or prolonged immobility)
2. Do not use inferior vena cava filters routinely in patients with acute venous thromboembolism

- workup
  - initial
    - CBC, blood smear, coagulation studies, liver/renal function, urinalysis, and hemolysis markers (if anemic)
    - malignancy history, age appropriate cancer screening
    - serology: APLA
  - post-treatment (or ≥6 wk, as protein levels depleted/consumed by clot)
    - antithrombin (not on heparin)
    - proteins C, S (not on warfarin)
- note: most of these tests do not change management, and a negative test does not rule out a hypercoagulable state
  - thus, more focus on the reversible/treatable causes (APLA, cancer, etc.)

## SELECTED CAUSES OF HYPERCOAGULABILITY

### Activated Protein C Resistance (Factor V Leiden)
- most common cause of hereditary thrombophilia
- 3-7% of European Caucasian population are heterozygotes
- point mutation in the Factor V gene (R506Q) results in resistance to inactivation of Factor Va by activated protein C

### Prothrombin Gene Mutation (PT) G20210A
- 1-3% of European Caucasian population are heterozygotes
- G to A transposition at nucleotide position 20210 of the prothrombin gene promoter region results in increased levels of prothrombin, thus increased thrombin generation

### Protein C and Protein S Deficiency
- protein C inactivates Factor Va and VIIIa using protein S as a cofactor
- protein C deficiency
  - homozygous or compound heterozygous: neonatal purpura fulminans
  - heterozygous
    - type I: decreased protein C levels
    - type II: decreased protein C activity
  - acquired: liver disease, sepsis, DIC, warfarin, and certain chemotherapeutic agents
  - 1/3 of patients with warfarin necrosis have underlying protein C deficiency
- protein S deficiency
  - type I: decreased free and total protein S levels
  - type II: decreased protein S activity
  - type III: decreased free protein S levels
  - acquired: liver disease, DIC, pregnancy, nephrotic syndrome, inflammatory conditions, and warfarin

### Antithrombin Deficiency
- antithrombin slowly inactivates thrombin in the absence of heparin, rapidly inactivates thrombin in the presence of heparin
- autosomal dominant inheritance, urinary losses in nephrotic syndrome, or reduced synthesis in liver disease
- diagnosis must be made outside window of acute thrombosis and anticoagulation treatment (acute thrombosis, heparin, systemic disease all decrease antithrombin levels)
- deficiency may result in resistance to unfractionated heparin (LMWH may be considered, with monitoring of anti-Xa levels)
  - heparin resistance: suspect if >35,000 units of UFH required during 24 h use

### Elevated Factor VIII Levels
- an independent marker of increased incident and recurrent thrombotic risk, but levels can also be increased in numerous states as an acute phase reactant, therefore its clinical use is controversial

### Congenital Dysfibrinogenemia
- may predispose to thromboembolic disease, bleeding or both

### Disorders of Fibrinolysis
- includes congenital plasminogen deficiency, tissue plasminogen activator deficiency, although association with VTE risk is not clear

### Antiphospholipid Antibody Syndrome (APS)
- definition: ≥1 clinical and ≥1 laboratory criteria
  - clinical: arterial or venous thrombosis, recurrent (>3) early pregnancy losses <10 wk, one late fetal loss ≥10 wk (morphologically normal), or premature birth before 34 wk due to (pre)eclampsia or placental insufficiency
  - laboratory (must be confirmed on two occasions, tested ≥12 wk apart): anticardiolipin antibodies, anti-β2 glycoprotein-I antibody, or lupus anticoagulant
- mechanism: not well understood, antibodies interact with platelet membrane phospholipid causing increased activation; can also interfere with thrombin regulation, fibrinolysis, and inhibit the protein C pathway
- see Rheumatology, RH13



**Common Causes of Hypercoagulability**

**CALM APES**
Protein **C** deficiency
**A**ntiphospholipid **A**b
Factor V **L**eiden
**M**alignancy
**A**ntithrombin deficiency
**P**rothrombin G20210A
Increased Factor **VIII** (**E**ight)
Protein **S** deficiency



**Causes of Both Venous and Arterial Thrombosis include:**
- Antiphospholipid antibodies
- Myeloproliferative neoplasms
- Heparin-induced thrombocytopenia
- Distal venous clot with patent foramen ovale
- Paroxysmal nocturnal hemoglobinuria



Protein C, protein S, and ATIII are decreased during acute thrombosis – therefore to test for deficiency, must be tested outside of this time period



**Malignancy is a common cause of acquired hypercoagulability**
**Workup should include:**
- Complete history and physical
- Routine blood work
- Urinalysis
- CXR
- Age appropriate screening: mammogram, Pap, PSA, colonoscopy
- Close follow-up
- No benefit with CT imaging



Although lupus anticoagulant prolongs PTT, this is a misnomer, as its main clinical feature is thrombosis

# Venous Thromboembolism

## Definition
- thrombus formation and subsequent inflammatory response in a superficial or deep vein
- superficial thrombophlebitis, deep vein thrombosis (DVT), and pulmonary embolism (PE)
- thrombi propagate in the direction of blood flow (commonly originating in calf veins)
- more common in lower extremity than upper extremity
- incidence ~1% if age >60 yr
- most important sequelae are pulmonary embolism (~50% chance with proximal DVT) and chronic venous insufficiency

## Etiology (Virchow's Triad)
- endothelial damage
  - exposes endothelium to prompt hemostasis
  - leads to decreased inhibition of coagulation and local fibrinolysis
- venous stasis
  - immobilization (post-MI, CHF, stroke, and post-operative) inhibits clearance and dilution of coagulation factors
- hypercoagulability
  - inherited (see *Hypercoagulable Disorders*, H33)
  - acquired
    - age (risk increases with age)
    - surgery (especially orthopedic, thoracic, GI, and GU)
    - trauma (especially fractures of spine, pelvis, femur or tibia, and spinal cord injury)
    - neoplasms (especially lung, pancreas, colon, rectum, kidney, and prostate)
    - blood dyscrasias (myeloproliferative neoplasms, especially PV, ET), PNH, and hyperviscosity (multiple myeloma, polycythemia, leukemia, and sickle cell disease)
    - prolonged immobilization (CHF, stroke, MI, and leg injury)
    - hormone related (OCP, HRT, and SERMs)
    - pregnancy
    - APS
    - heart failure (risk of DVT greatest with right heart failure and peripheral edema)
- idiopathic (10-20% are later found to have cancer)

## Clinical Features of DVT
- absence of physical findings does not rule out disease
- unilateral leg edema, erythema, warmth, and tenderness; purple-blue colour
- palpable cord (thrombosed vein)
- phlegmasia alba dolens (white appearance) and phlegmasia cerula dolens (acute pain and edema) with massive thrombosis
- Homan's sign (pain with foot dorsiflexion) is unreliable

## Differential Diagnosis of DVT
- muscle strain or tear, lymphangitis or lymph obstruction, venous valvular insufficiency, ruptured popliteal cysts, cellulitis, and arterial occlusive disease

## Investigations for DVT
- D-dimer test only useful to rule out DVT if negative with low clinical suspicion of disease and no other acute medical issues
- doppler ultrasound is most useful diagnostic test for DVT
  - sensitivity and specificity for proximal DVT ~95%
  - sensitivity for calf DVT ~70%
- other non-invasive tests include MRI and impedence plethysmography
- venography is the gold standard, but is expensive, invasive, and higher risk
- CTPA or V/Q scan if PE suspected

## Post-Thrombotic Syndrome
- development of chronic venous stasis signs and symptoms secondary to a deep venous thrombosis
- symptoms: pain, venous dilatation, edema, pigmentation, skin changes, and venous ulcers
- clinical severity can be estimated based on the Villalta score
- large impact on quality of life following a DVT
- treatment: extremity elevation, exercise, continuous compression stockings, intermittent pneumatic compression therapy, and skin/ulcer care
- for clinical features and treatment of PE, see Respirology, R19

**Risk of VTE in Hospitalized Patients Receiving Ineffective Antithrombotic Therapy**

| Risk Factor | RR (95% CI) | P-value |
|---|---|---|
| Age >75 yr | 1.79 (1.18-2.71) | 0.007 |
| Cancer | 1.58 (1.01-2.51) | |
| Previous VTE | 1.67 (1.01-2.77) | 0.08 |
| Obesity | 0.94 (0.59-1.51) | 0.91 |
| Hormone therapy | 0.51 (0.08-3.38) | 0.70 |
| Heart failure | 0.08 (0.72-1.62) | 0.82 |
| NYHA III | 0.89 (0.55-1.43) | 0.72 |
| NYHA IV | 1.48 (0.84-2.6) | 0.27 |
| Acute infectious disease | 1.50 (1.00-2.26) | 0.06 |
| Acute rheumatic disease | 1.45 (0.84-2.50) | 0.27 |

Source: *JAMA* 2004;164:963-968

**Virchow's Triad**
- Endothelial damage
- Stasis
- Hypercoagulability

**Wells' Score for DVT Criteria (Score)**
- Paralysis, paresis, or recent orthopedic casting of lower extremity (1)
- Recently bedridden (>3 d) or major surgery within past 4 wk (1)
- Localized tenderness in deep vein system (1)
- Swelling of entire leg (1)
- Calf swelling >3 cm than other leg (measured 10 cm below the tibial tuberosity) (1)
- Pitting edema greater in the symptomatic leg (1)
- Collateral non-varicose superficial veins (1)
- Active cancer or cancer treated within 6 mo (1)
- Alternative diagnosis more likely than DVT (e.g. Baker's cyst, cellulitis, muscle damage, superficial venous thrombosis) (-2)

**Total Score Interpretation**
3-8: High probability, 1-2: Moderate probability, -2-0: Low probability

**Modified Wells Score**
Same as above except with 1 additional point for a history of DVT or major surgery within past 12 wk, and the score interpretation is DVT likely for ≥ 2 points and DVT unlikely for ≤1 point. D-dimer is ordered for DVT unlikely patients to fully rule out DVT which can help reduce unnecessary ultrasounds

**Low-Molecular-Weight Heparin vs. Coumadin® for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer**
NEJM 2003;349:146-153
**Study**: RCT comparing the efficacy of LMWH (dalteparin) with an oral anti-coagulant agent (coumarin) in preventing recurrent thrombosis in patients with cancer.
**Methods**: Patients with cancer who had acute, symptomatic proximal DVT, PE, or both were randomly assigned to either dalteparin or coumarin treatment for 6 mo.
**Results**: 27 of 336 patients in the dalteparin group had recurrent VTE versus 53 of 336 patients in the coumarin group (hazard ratio, 0.48; p=0.002). The probability of recurrent thromboembolism at 6 mo was 9% and 17% in dalteparin and coumarin groups respectively. There was no significant difference in bleeding rates. The mortality rate was 39% in the dalteparin group and 41% in the coumarin group.
**Conclusions**: In patients with cancer and acute VTE, dalteparin was more effective than coumarin in decreasing the risk of recurrent thromboembolism without increasing the risk of bleeding.

# Approach to Treatment of Venous Thromboembolism

## Purpose

- prevent further clot extension (3 mo duration is optimal)
- prevent acute pulmonary embolism (occurs in up to 50% of untreated patients)
- reduce the risk of recurrent thrombosis (duration depends on presence of other risk factors)
- treatment of massive ileofemoral thrombosis with acute lower limb ischemia and/or venous gangrene (phlegmasia cerulea dolens)
- limit development of late complications (e.g. postphlebitic syndrome, chronic venous insufficiency, and chronic thromboembolic pulmonary HTN)

## Initial Treatment

- low molecular weight heparin (LMWH)
  - administered SC, at least as effective as UFH with a lower bleeding risk
  - advantages: predictable dose response and fixed dosing schedule; lab monitoring not required; <1% HIT; safe and effective outpatient therapy
  - disadvantages: only partially reversible by protamine, long-term use associated with osteoporosis, costly!
  - renally cleared – must adjust dose in patients with renal dysfunction
- unfractionated heparin (UFH)
  - in patient with average risk of bleed; use hospital-based nomograms that use bleeding risk and patient weight to determine appropriate dose
  - advantages: rapidly reversible by protamine
  - disadvantages: must monitor aPTT or heparin levels with adjustment of dose to reach therapeutic level (~2x normal value); monitor platelet counts for development of HIT
- alternatives to LMWH and UFH
  - direct thrombin inhibitors (hirudin, lepirudin, argatroban) and direct factor Xa inhibitors (apixaban, rivaroxaban)
  - thrombolytic drugs (e.g. streptokinase, tPA) reserved for acute limb/life-threatening thrombosis, and low bleeding risk

## Long-Term Treatment

- anticoagulation therapy
  - warfarin
    - standard treatment; should be initiated with heparin overlap: dual therapy for at least 48 hours with INR >2, due to initial prothrombotic state secondary to warfarin's inhibition of natural anticoagulants protein C/S, half-life of vitamin K factors and risk of warfarin-induced skin necrosis
    - INR: warfarin dosed to maintain INR at 2-3, monitor twice weekly for 1-2 wk
      - discontinue heparin after INR>2.0 for 2 consecutive days
  - direct oral anticoagulants (DOACs)
    - apixaban or rivaroxaban; with no laboratory monitoring required, patients with CrCl >25 ml/min (apixaban) or 30 ml/min (rivaroxaban)
    - dabigatran (factor IIa inhibitor): LMWH or IV heparin for at least 5-10 d before initiating dabigatran, patients with CrCl >30 mL/min
    - important drug interactions to consider for DOACs (no relevant food interactions however)
  - cancer patients: LMWH more effective than warfarin at preventing recurrence of venous thrombosis in cancer patients; increasing evidence to support DOACs in cancer-associated thrombosis
- duration of anticoagulant treatment
  - provoked VTE with transient risk factor: 3 mo
  - provoked VTE with ongoing risk factor: consider indefinite therapy with annual reassessment
  - first unprovoked VTE: at least 3 mo, subsequent reassessment
  - unprovoked proximal DVT or PE: consider indefinite therapy with annual reassessment
  - second unprovoked VTE: consider indefinite therapy
  - cancer-associated DVT: at least 3 mo, longer if continued evidence of cancer
- IVC filters
  - temporary filter indicated only if acute DVT (<4 wk) with significant contraindications to anticoagulant therapy (i.e. active bleeding) or if require interruption of anticoagulation (i.e. for urgent surgery)
  - must be retrieved once safe to do so as filter is pro-thrombotic in the long-term (consider anticoagulation if not retrieved)
- special considerations
  - pregnancy: treat with LMWH during pregnancy, then LMWH or warfarin for 6 wk post-partum (minimum total anticoagulation time of 3-6 mo, but must include 6 wk post-partum, as this is a high risk period); avoid warfarin in pregnancy due to teratogenicity, avoid DOAC in pregnancy (due to lack of data) and if breastfeeding in postpartum period



**Duration of Treatment with Vitamin K Antagonists in Symptomatic Venous Thromboembolism**
Cochrane DB Syst Rev 2009;CD001367
**Study**: Meta-analysis of 8 RCTs (2994 patients) comparing different durations of treatment with vitamin K antagonists in patients with symptomatic VTE.
**Results**: In patients treated with vitamin K antagonists for a prolonged period, the reduction in risk of recurrent VTE remained consistent regardless of the period of time since the index event (OR 0.18; 95% CI 0.13-0.26). In addition, there was no observed excess of VTE recurrences following cessation of prolonged treatment (i.e. rebound phenomenon) (OR 1.24; 95% CI 0.91-1.69). However, patients who received prolonged treatment had a persistent increase in their risk of major bleeding complications (OR 2.61; 95% CI 1.48-4.61).
**Conclusion**: Prolonged treatment with vitamin K antagonists leads to a consistent reduction in the risk of recurrent VTE for as long as therapy is continued. Therapy should be discontinued when the risk of harm from major bleeding (which remains constant over time) is of greater concern than the absolute risk of recurrent VTE (which declines over time). No specific recommendation was made regarding optimal duration of treatment.



**Common Medications that Interact with Warfarin**
- Acetaminophen (interference with vitamin K metabolism)
- Allopurinol
- NSAIDs (GI injury)
- Fluconazole
- Metronidazole
- Sulfamethoxazole
- Tamoxifen



**Initiation of Warfarin Therapy Requires Bridging with Heparin Therapy for 4-5 Days**
- 10 mg loading dose (for example) of warfarin causes a precipitous decline in protein C levels in first 36 h resulting in a transient hypercoagulable state
- Warfarin decreases Factor VII levels in first 48 h, INR is prolonged (most sensitive to Factor VII levels), however full antithrombotic effect is not achieved until Factor IX, X, and II are sufficiently reduced (occurs after ~4 d)



**Low Risk Surgical Patients**
<40 yr, no risk factors for VTE, general anesthetic (GA) <30 min, minor elective, abdominal, or thoracic surgery

**Moderate Risk Surgical Patients**
>40 yr, >1 risk factor for VTE, GA >30 min

**High Risk Surgical Patients**
>40 yr, surgery for malignancy or lower extremity orthopedic surgery lasting >30 min, inhibitor deficiency, or other risk factor

**High Risk Medical Patients**
Heart failure, severe respiratory disease, ischemic stroke and lower limb paralysis, confined to bed and have >1 additional risk factor (e.g. active cancer, previous VTE, sepsis, acute neurologic disease, IBD)

- surgery: avoid elective surgery in the first 3 mo after a venous thromboembolic event
  - pre-operatively: IV heparin may be used up to 4-6 h pre-operatively
  - perioperatively: warfarin or DOACs discontinued for at least 3-5 d pre-operatively (consider mechanism of drug clearance)
  - post-operatively: IV heparin, LMWH, DOAC can be used for anticoagulation (consult with surgeon prior to re-initiation)
  - for patients at high risk for thromboembolism (VTE <12 wk, recurrent VTE, antiphospholipid antibody syndrome, atrial fibrillation with prior stroke, and mechanical heart valve), IV heparin or LMWH (bridging) should be considered before and after the procedure while the INR is below 2.0

### Prophylaxis

- consider for those with a moderate to high risk of thrombosis without contraindications
- non-pharmacological measures include: early ambulation, elastic compression stockings (TEDs), and intermittent pneumatic compression (IPC)
- UFH 5000 IU SC bid, UFH 5000 IU SC tid or LMWH as per hospital protocol (e.g. enoxaparin 40 mg SC daily, dalteparin 5000 U SC qid), and DOACs for orthopedic surgery thromboprophylaxis

**Table 30. Contraindications of Anticoagulant Therapy**

| Absolute Contraindications to Treatment | Relative Contraindications to Treatment |
|---|---|
| Active bleeding | Mild-moderate bleeding diathesis or thrombocytopenia |
| Severe bleeding diathesis or platelet count <20 x $10^9$/L (<20,000/$mm^3$) | Brain metastases |
| Intracranial bleeding | Recent major trauma |
| Neurosurgery or ocular surgery within 10 d | Recent stroke |
| | Major abdominal surgery within past 2 d |
| | GI/GU bleeding within 1-4 d |
| | Endocarditis |
| | Severe hypertension (sBP >200 or dBP >120) |

### Treatment of Pulmonary Embolism

- see Respirology, R19

# Hematologic Malignancies and Related Disoders

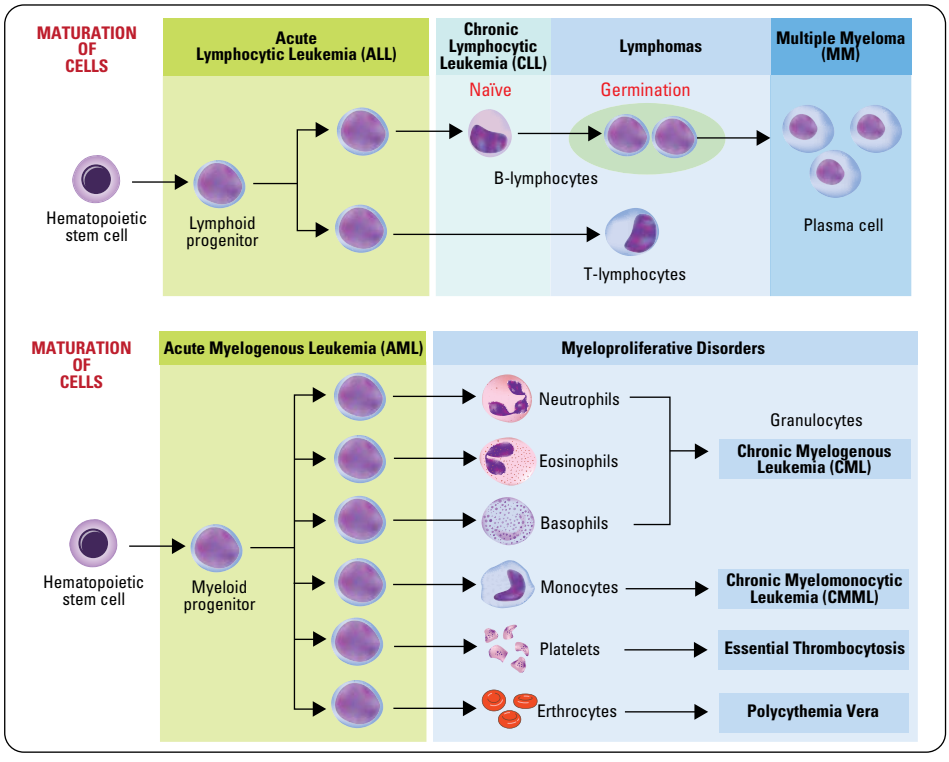



**Figure 15. Hematopoietic derivation of hematologic disorders**

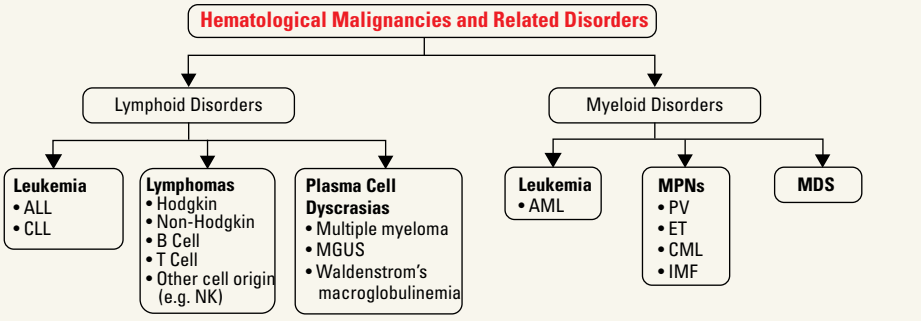
**Typical Age of Presentation of Leukemias**
- ALL: Children and older adults
- CML: 40-60 yr
- AML, CLL: >60 yr

**Leukemia:** malignant cells arise in bone marrow that may spread elsewhere (including blood, lymph nodes, and lymphoid tissue)
**Lymphoma:** malignant cells arise in lymph nodes and lymphoid tissues that may spread elsewhere (including blood and bone marrow)
**BUT** the location where the malignant cells are found does not solely define the type of hematologic malignancy – classified based on the characteristics of the cell (histology, histochemistry, immunophenotyping, cytogenetics, molecular changes)

**Acute Leukemia**
**Definition (WHO):** presence of 20% blast cells or greater in the peripheral blood or bone marrow at presentation
**Classification:** divided into myeloid (AML) and lymphoid (ALL) depending on whether blasts are myeloblasts or lymphoblasts, respectively

Auer rods are pathognomonic for AML

**Basic initial workup for all hematological malignancies:**
1. ALL CHILDBEARING WOMEN must have a b-HCG pre initiation of treatment of any cancer diagnosis
2. ALL PATIENTS MUST HAVE HBsAb, HBsAg, HBcAb collected irrespective of cancer diagnosis and must be treated to avoid reactivation
3. All aggressive lymphoma patients must be screened for HIV
4. All patients must be screened for TB risk factors




ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; ET = essential thrombocythemia; IMF = idiopathic myelofibrosis; MDS = myelodysplastic syndromes; MGUS = monoclonal gammopathy of unknown significance; MPN = myeloproliferative neoplasms; PV = polycythemia vera

**Figure 16. Overview of hematologic malignancies and related disorders**

# Myeloid Malignancies

## Acute Myeloid Leukemia

### Definition
- rapidly progressive malignancy characterized by failure of myeloid cells to differentiate beyond blast stage

### Epidemiology
- incidence increases with age; median age of onset is 65 yr old; 80% of acute adult leukemias
- accounts for 10-15% of childhood leukemias

### Risk Factors
- male, older age, smoking, obesity, myelodysplastic syndromes (MDS), benzene, radiation, Down Syndrome, alkylating agents and radiation therapy as treatment for previous malignancy

### Pathophysiology
- etiology subdivided into:
  - primary: *de novo*
  - secondary: hematologic malignancies (e.g. myeloproliferative disorders and MDS) or previous chemotherapeutic agents (e.g. alkylating agents)
- uncontrolled growth of blasts in marrow leads to:
  - suppression of normal hematopoietic cells
  - appearance of blasts in peripheral blood – risk of leukostasis
  - accumulation of blasts in other sites (e.g. skin, gums)
  - metabolic consequences; tumour lysis syndrome

### Clinical Features
- signs and symptoms develop over a period of weeks
- manifestations of bone marrow failure
  - anemia, thrombocytopenia (associated with DIC in promyelocytic leukemia), neutropenia (even with normal WBC), leads to infections, and fever
- accumulation of blast cells in marrow
  - skeletal pain, bony tenderness (especially sternum)
- organ infiltration
  - gingival hypertrophy (particularly myelomonocytic leukemia) – may present to dentist first
  - extramedullary involvement
  - hepatosplenomegaly (in ALL)
  - lymphadenopathy (not marked in ALL)
  - gonads (in ALL)
  - skin: leukemia cutis or myeloid sarcoma
  - eyes: hemorrhages and/or whitish plaques, Roth spots, cotton wool spots, and vision changes (uncommon)
- leukostasis/hyperleukocytosis syndrome (medical emergency)
  - large numbers of blasts interfere with circulation and lead to hypoxia and hemorrhage – can cause diffuse pulmonary infiltrates, CNS bleeding, respiratory distress, altered mental status, and priapism
  - associated with AML more than ALL
- metabolic effects; aggravated by treatment
  - increased uric acid → nephropathy, gout
  - release of phosphate → decreased $Ca^{2+}$, decreased $Mg^{2+}$
  - release of procoagulants → DIC (higher risk in acute promyelocytic leukemia)
- tumour lysis syndrome
  - hyperkalemia pre-treatment from blastic proliferation $K^+$ after treatment (from lysed cells). Note – some forms of AML can present with hypokalemia due to secreted muraimdase that causes $K^+$ wasting from renal tubules

### Investigations
- blood work
  - CBC: anemia, thrombocytopenia, variable WBC (most often cytopenias + blasts)
  - INR, aPTT, fibrin degradation products (FDP), fibrinogen (in case of DIC)
  - increased LDH, increased uric acid, increased $PO_4^{3-}$ (released by leukemic blasts), decreased $Ca^{2+}$, in/decreased $K^+$
  - baseline renal and liver function tests
  - if considering treatment: screen for HepB, HepC, HIV, CMV
- peripheral blood film – circulating blasts with Auer rods (azurophilic granules) are pathognomonic for AML
- bone marrow aspirate for definitive diagnosis
  - blast count: AML >20% (normal is <5%)
  - morphologic, cytochemical, and/or immunophenotypic features are used to establish lineage and maturation
- CXR to rule out pneumonia; ECG, MUGA scan prior to chemotherapy (cardiotoxic)

### Treatment
- mainstay of treatment is chemotherapy (rapidly fatal without treatment)
- all AML subtypes are treated similarly, except acute promyelocytic leukemia (APL) with t(15:17) translocation

**1. Induction**: chemotherapy to induce complete remission of AML
  - several possible regimens
  - patients with poor response to initial induction therapy – worse prognosis
  - must ensure reversal of DIC, platelet transfusions if <10

**2. Consolidation**: to prevent recurrence
  - intensive consolidation chemotherapy
  - stem cell transplantation – allogeneic (younger patients with better performance status)

- supportive care
  - fever: C&S of all orifices, CXR, and start antibiotics
  - platelet and RBC transfusions ± EPO
  - prevention and treatment of metabolic abnormalities
    - allopurinol, rasburicase for prevention of hyperuricemia
  - leukostasis
    - needs immediate cytoreductive therapy (i.e. hydroxyurea)
  - treatment strategy for APL
    - APL is an emergency as DIC is often presented at diagnosis
    - all-trans-retinoic acid (ATRA) added to induce differentiation; arsenic trioxide and ATRA combination therapy for APL is non-inferior to traditional chemotherapy

**Cure:** survival that parallels age-matched population
**Complete Remission:** tumour load below threshold of detectable disease (normal peripheral blood film, normal bone marrow with <5% blasts, normal clinical state)

### Prognosis
- achievement of first remission
  - 70-80% if ≤60 yr old, 50% if >60 yr old
  - median survival 12-24 mo
  - prognosis is most related to 1) cytogenetics; classified as favourable, intermediate, or adverse and 2) molecular studies (i.e. $NPM1^+$/FLT3- mutations)
  - prognosis depends on cytogenetics, age, performance status, prior cytotoxic agents, or radiation therapy

## Myelodysplastic Syndromes

### Definition
- heterogeneous group of malignant stem cell disorders characterized by dysplastic and ineffective blood cell production resulting in peripheral cytopenias, and a variable risk of transformation to acute leukemias
- syndromes defined according to World Health Organization (WHO) classifications

MDS is a cause of macrocytic anemia

### Pathophysiology
- disordered maturation: ineffective hematopoiesis despite presence of adequate numbers of progenitor cells in bone marrow (usually hypercellular); formed elements sometimes exhibit morphological and functional defects
- intramedullary apoptosis: programmed cell death within bone marrow
- both processes lead to reduced mature cells in periphery
- <30% develop AML

### Risk Factors
- elderly, post-chemotherapy, exposures (benzene, tobacco, radiation), inherited genetic abnormalities
- incidence: 50 persons per million per year, rises to 200-400 per million per year for age 70 or older

### Clinical Features
- highly variable, commonly presents with symptoms of anemia (fatigue and dyspnea), thrombocytopenia (bruising, bleeding or petechiae), and neutropenia (recurrent infections) over months-years

### Investigations
- diagnosed by:
  - anemia ± thrombocytopenia ± neutropenia
  - CBC and peripheral blood film
  - RBC: usually macrocytic with oval shaped red cells (macro-ovalocytes), decreased reticulocyte count
  - WBC: decreased granulocytes and abnormal morphology (e.g. bi-lobed or unsegmented nuclei = Pelger abnormality)
  - platelets: thrombocytopenia, abnormalities of size, and cytoplasm (e.g. giant hypogranular platelets)
- bone marrow aspirate and biopsy with cytogenetic analysis required for definitive diagnosis
  - bone marrow: dysplastic and often normocellular/hypercellular
  - cytogenetics: high risk (partial or total loss of chromosome 7) and complex (>3 abnormalities)

### Treatment
- low risk of transformation to acute leukemia (IPSS-R Very Low or Low)
  - erythropoietin stimulating agents weekly is first line in reducing transfusion requirements (EPO level must be <500)
  - hypomethylating agents: decitabine and azacitidine
  - if 5q deletion based on cytogenetics: lenalidomide PO
  - supportive care: RBC and platelet transfusion (consider iron chelation if frequent RBC transfusions)
- high risk of transformation to acute leukemia (IPSS-R intermediate, high or very high)
  - supportive care
  - consider stem cell transplantation according to patient factors (age, frailty, overall health)
  - epigenetic therapy: DNA methyltransferase inhibitors (e.g. 5-azacytidine), histone deacetylase inhibitors

### Prognosis
- Revised International Prognostic Scoring System (IPSS-R) uses 5 factors to estimate mean survival:
  - cytology, % bone marrow blasts, hemoglobin, platelets, and absolute neutrophil count
  - based on the calculated score, a patient's MDS prognostic risk is "Very Low", "Low", "Intermediate", "High", or "Very High" with a mean survival of 8.7, 5.3, 3.0, 1.6, and 0.8 yr, respectively

**Use of Epoetin and Darbepoetin in Patients with Cancer**
Blood 2008;111:25-41
Clinical practice guideline update by American Societies of Hematology and Clinical Oncology (2010).
**Initial Recommendations**
1. Initiate an erythropoiesis-stimulating agent (ESA) when hemoglobin (Hb) is 100 g/L (10 g/dL) in patients with palliative chemotherapy-associated anemia to decrease the need for transfusions.
2. Discontinue ESAs when patient not responding to treatment beyond 6-8 wk.
3. Monitor iron stores and supplement iron intake for ESA-treated patients when necessary.
4. Use ESAs cautiously with chemotherapy or in patients with an elevated risk for thromboembolic complications.
5. It is not recommended that ESA be used for therapy in patients with cancer who are not receiving chemotherapy, as it increases thromboembolic risks and lowers survival rate. Patients with low-risk myelodysplasia are an exception.

# Myeloproliferative Neoplasms

### Definition
- clonal myeloid stem cell abnormalities leading to overproduction of one or more cell lines (leading to abnormalities in erythrocytes, platelets, and other cells of myeloid lineage)

### Epidemiology
- mainly middle-aged and older patients (peak 60-80 yr)

### Prognosis
- may develop marrow fibrosis with time
- all disorders may progress to AML

**Myelodysplastic Syndromes**
ineffective maturation
**Myeloproliferative Neoplasms**
overproduction of mature cells

**Table 31. Chronic Myeloproliferative Disorders**

| | CML | PV | IMF | ET |
|---|---|---|---|---|
| **Hct** | ↓/N | ↑↑ | ↓ | N |
| **WBC** | ↑↑ | ↑ | ↑/↓ | N |
| **Plt** | ↑/↓ | ↑ | ↑/↓ | ↑↑↑ |
| **Marrow Fibrosis** | ± | ± | +++ | ± |
| **Splenomegaly** | +++ | + | +++ | + |
| **Hepatomegaly** | + | + | ++ | – |
| **Genetic Association** | *bcr-abl* mut. (95+%) | JAK2 mut. (96%) | JAK2 mut. (~50%)<br>CALR mut (~30%) | JAK2 mut. (~50%)<br>CALR mut (~30%) |

CML = chronic myeloid leukemia; ET = essential thrombocythemia; IMF = idiopathic myelofibrosis; PV = polycythemia vera CALR = Calreticulin

# Chronic Myeloid Leukemia

Basophilia is uncommon in other medical conditions

### Definition
- myeloproliferative disorder characterized by increased proliferation of the granulocytic cell line without the loss of their capacity to differentiate

### Epidemiology
- occurs in any age group (mostly middle age to elderly) with a median age of 65 yr

### Pathophysiology
- Philadelphia chromosome (Ph)
  - translocation between chromosomes 9 and 22
  - the c-Abl proto-oncogene is translocated from chromosome 9 to "breakpoint cluster region" (BCR) of chromosome 22 to produce BCR-Abl fusion gene, an constitutively active tyrosine kinase

## Clinical Features

- 3 clinical phases
  - chronic phase: 85% diagnosed here
    - few blasts (<10%) in peripheral film
    - ± slightly elevated eosinophils and basophils
    - no significant symptoms
  - accelerated phase: impaired neutrophil differentiation
    - circulating blasts (10-19%) with increasing peripheral basophils (pruritus)
    - CBC: thrombocytopenia <100 x $10^9$/L
    - cytogenetic evidence of clonal evolution
    - worsening constitutional symptoms and splenomegaly (extramedullary hematopoiesis)
  - blast crisis: more aggressive course, blasts fail to differentiate
    - blasts (>20%) in peripheral blood or bone marrow; reflective of acute leukemia (1/3 ALL, 2/3 AML)
- clinical feature
  - 20-50% of patients are asymptomatic when diagnosed (incidental lab finding)
  - nonspecific symptoms
    - fatigue, weight loss, malaise, excessive sweating, fever
  - secondary to splenic involvement
    - early satiety, LUQ pain/fullness, shoulder tip pain (referred)
    - splenomegaly (most common physical finding)
  - anemia
  - bleeding: secondary to platelet dysfunction
  - pruritus, PUD: secondary to increased blood histamine
  - leukostasis, priapism, encephalopathy (rare): secondary to very elevated WBC (rare)

**Chronic Myeloproliferative Neoplasias: Six Year Follow-Up of Patients Receiving Imatinib for the First-Line Treatment of CML**
Leukemia 2009;23:1054-1061
**Study**: The Randomized Study of Interferon vs. STI571 (IRIS) trial enrolled patients with chronic phase chronic myeloid leukemia (CML-CP) to either imatinib (n=533) or interferon-α (IFN -α) plus cytarabine (n=553).
**Results**: Assessing the imatinib arm specifically at the sixth year point, there were no reports of disease progression to accelerated phase (AP) or blast crisis (BC), toxicity profile was unchanged, and cytogenetic response rate was 82%. Estimated event-free survival was 83% and rate of freedom from progression to AP and BC was 93%.
**Conclusion**: This 6-year update of IRIS demonstrates the efficacy and safety of imatinib as first-line therapy for CML patients.

## Investigations

- elevated WBC, decreased/normal RBC, increased/decreased platelets, increased basophils
  - WBC differential shows a bimodal distribution, with predominance of myelocytes and neutrophils
- peripheral blood film
  - leukoerythroblastic picture (immature red cells and granulocytes present, e.g. myelocytes and normoblasts)
  - presence of different mid-stage progenitor cells differentiates it from AML
- bone marrow
  - myeloid hyperplasia with left shift, increased megakaryocytes, mild fibrosis
- molecular and cytogenetic studies of bone marrow or peripheral blood for Philadelphia chromosome
- abdominal imaging for spleen size

Detection of the *bcr-abl* fusion gene is a diagnostic test for CML (present in over 90% of patients)

## Treatment

- **prophylactic:** allopurinol
- **chronic phase**
  - imatinib mesylate inhibits proliferation and induces apoptosis by inhibiting tyrosine kinase activity in cells positive for bcr-abl. 2nd/ 3rd generation can be trialed based on patient co-morbidities as first line.
    - if loss of response or intolerance (~40%), trial of 2nd or 3rd generation tyrosine kinase inhibitors (TKIs): dasatinib, nilotinib, or bosutinib. Note: Ponatinib only provided for the T315I mutation.
  - interferon-α: may improve response to tyrosine kinase inhibitors; typically now only used for pregnant patients
  - hydroxyurea in palliative setting to reduce WBC
- **accelerated phase or blast phase**
  - for imatinib-naive patients, use imatinib
  - refer for clinical trial or 2nd/3rd generation TKI and prepare for allogeneic stem cell transplant patients, in blast phase typically get standard AML induction
- stem cell transplantation may be curative: to be considered in young patients who do not meet therapeutic milestones
- treatment success is monitored based on therapeutic milestones
  - hematologic: improved WBC and platelet counts, reduced basophils
  - cytogenetic: undetectable Philadelphia-chromosome in the bone marrow
  - molecular: reduction/absence of bcr-abl transcripts in periphery and marrow

## Prognosis

- survival dependent on response
  - those achieving complete cytogenetic response (CCR) on imatinib by 18 mo of therapy: 6 yr overall survival >90%
  - those who do NOT achieve CCR on imatinib: 6 yr overall survival of 66%
- acute phase (blast crisis – usually within 3-5 yr)
  - 2/3 acute phase CML have cellular features similar to AML
    - unresponsive to remission induction
  - 1/3 acute phase CML have cellular features similar to ALL
    - remission induction (return to chronic phase) achievable

# Polycythemia Vera

## Definition
- stem cell disorder characterized by elevated RBC mass (erythrocytosis) ± increased white cell and platelet production
- diagnosis (WHO 2016) requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion
  - Major Criteria
    1. hemoglobin >165 g/L in men, >160 g/L in women, OR Hct >49% in men or >48% in women, OR increased red cell mass (>25% above mean normal predicted value)
    2. bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation
    3. presence of JAK2 V617F or JAK2 exon 12 mutation
  - Minor Criterion
    1. serum erythropoietin level below reference range for normal (must have at least two major criteria if using erythropoietin level)

## Clinical Features
- symptoms are secondary to high red cell mass and hyperviscosity (see *Erythrocytosis*, H6)
- thrombotic complications: DVT, PE, Budd-Chiari (hepatic vein thrombosis), portal vein thrombosis, thrombophlebitis, increased incidence of stroke, and MI
  - due to increased blood viscosity, increased platelet number and/or activity
  - bleeding complications: epistaxis, gingival bleeding, ecchymoses, and GI bleeding
  - if high platelet counts: associated with acquired vWD
- erythromelalgia (burning pain in hands and feet and erythema of the skin)
  - associated with platelets >400 x $10^9$/L
  - pathognomonic microvascular thrombotic complication in PV and ET
- pruritus, especially after warm bath or shower (40%) due to cutaneous mast cell degranulation and histamine release
- epigastric distress, PUD
  - due to increased histamine from tissue basophils, alterations in gastric mucosal blood flow due to increased blood viscosity
- gout (hyperuricemia), due to increased cell turnover
- characteristic physical findings
  - plethora (ruddy complexion) of face (70%), palms
  - splenomegaly (70%), hepatomegaly (40%)

## Investigations (see *Erythrocytosis*, H6)
- must rule out secondary polycythemia if high Epo level

## Treatment
- phlebotomy to keep hematocrit <45%
- hydroxyurea (prior thrombosis or symptoms, severe coronary artery disease, refractory to phlebotomy)
- low-dose Aspirin® (for antithrombotic prophylaxis, will also treat erythromelalgia)
- allopurinol: as needed
- antihistamines: as needed

## Prognosis
- 10-20 yr survival with treatment
- complicated by thrombosis, hemorrhage, leukemic transformation (AML)

Erythromelalgia is a pathognomonic microvascular thrombotic complication in PV and ET

**Cardiovascular Events and Intensity of Treatment in Polycythemia Vera**
NEJM 2013;368:22-33
**Study**: Prospective, RCT, mean follow-up of 28.9 mo. Blinding not described.
**Population**: 365 patients with JAK2-positive polycythemia vera being treated with phlebotomy, hydroxyurea, or both.
**Intervention**: Patients were randomized to a target hematocrit <45% (low-hematocrit group) or 45-50% (high-hemtocrit group).
**Outcome**: Composite of time until death from cardiovascular causes of major thrombotic events.
**Results**: The hazard ratio (HR) for the primary outcome was 3.91 (95% CI 1.45-10.53, p=0.007), while the HR for the primary outcome plus superficial venous thrombosis was 2.69 (95% CI 1.19-6.12, p=0.02) for the high-hematocrit vs. low-hematocrit group.
**Conclusions**: The hematocrit target of <45% was associated with a lower incidence of CV death, major thrombotic events, and superficial venous thrombosis in patients with polycythemia vera.

**Efficacy and Safety of Low-dose Aspirin® in Polycythemia Vera**
NEJM 2004;350:114-124
**Study**: Double-blind, placebo-controlled, RCT.
**Participants**: 518 patients with polycythemia vera (PV) with no clear indication for, or contraindication to, ASA therapy.
**Intervention**: Patients received either low-dose ASA 100 mg daily (n=253) or placebo (n=265) and were followed for up to 5 yr.
**Primary Outcome**: Cumulative rate of (I) nonfatal MI, nonfatal stroke, or death from cardiovascular causes and the cumulative rate of (II) the previous 3 plus PE and major venous thrombosis.
**Results**: Primary outcomes (I) and (II) were reduced with treatment compared to placebo (RR 0.41; p=0.09 and RR 0.4; p=0.03, respectively). There were no differences in overall or cardiovascular mortality and major bleeding episodes.
**Conclusion**: Low-dose ASA can safely prevent thrombotic complications in patients with PV.

# Idiopathic Myelofibrosis

## Definition
- excessive bone marrow fibrosis leading to marrow failure
- characterized by anemia, extramedullary hematopoiesis, leukoerythroblastosis, teardrop red cells in peripheral blood and hepatosplenomegaly

## Epidemiology
- rare, median age at presentation is 65 yr

## Pathophysiology
- abnormal myeloid precursor postulated to produce dysplastic megakaryocytes that secrete fibroblast growth factors
  - stimulates fibroblasts and stroma to deposit collagen in marrow
- increasing fibrosis causes early release of hematopoietic precursors leading to:
  - leukoerythroblastic blood film (primitive RBCs and WBCs present in blood)
  - migration of precursors to other sites: extramedullary hematopoiesis (leading to hepatosplenomegaly)

## Clinical Features
- anemia (severe fatigue is most common presenting complaint, pallor on exam in >60%)
- weight loss, fever, night sweats → secondary to hypermetabolic state
- splenomegaly (90%) → secondary to extramedullary hematopoiesis; may cause early satiety
- hepatomegaly (70%) → may get portal hypertension
- bone and joint pain → secondary to osteosclerosis, gout
- signs of extramedullary hematopoiesis (depends on organ involved)

Myelofibrosis can be either primary (idiopathic) or occur as a transformation of an antecedent PV or ET

A "leukoerythroblastic" blood film (RBC and granulocyte precursors) implies bone marrow infiltration with malignancy (e.g. leukemias, solid tumour metastases) or fibrosis (e.g. IMF)

IMF typically has a dry BM aspirate and teardrop RBCs (aspiration gives no blood cells)

### Investigations
- CBC: anemia, variable platelets, variable WBC
- biochemistry: increased ALP (liver involvement, bone disease), increased LDH (2º to ineffective hematopoiesis), increased uric acid (increased cell turnover), increased $B_{12}$ (2º to increased neutrophil mass)
- blood film: leukoerythroblastosis with teardrop RBCs, nucleated RBCs, variable polychromasia, large platelets, and megakaryocyte fragments
- molecular test: JAK2 (70%) and calreticulin (25%) mutations
- bone marrow aspirate: "dry tap" in as many as 50% of patients (no blood cells aspirated)
- bone marrow biopsy (essential for diagnosis): fibrosis, atypical megakaryocytic hyperplasia, thickening and distortion of the bony trabeculae (osteosclerosis)

### Treatment
- allogeneic stem cell transplant is potentially curative
- JAK2 inhibitors (Ruxolitinib)
- symptomatic treatment
  - transfusion for anemia
  - erythropoietin: 30-50% of patients respond
  - androgens for anemia (e.g. danazol has shown transient response with response rates of <30%)
  - hydroxyurea for splenomegaly, thrombocytosis, leukocytosis, and systemic symptoms
    - interferon-α (as second line therapy)
    - splenectomy (as third line therapy; associated with high mortality and morbidity)
  - radiation therapy for symptomatic extramedullary hematopoiesis, and symptomatic splenomegaly

### Prognosis
- Dynamic International Prognostic Scoring System (DIPSS) Plus for IMF uses 5 risk factors along with karyotype, platelet count, and transfusion status to predict survival
  - presence of constitutional symptoms; age >65; hemoglobin <100 g/L; leukocyte count >25,000/$mm^3$; circulating blast cells ≥1%
  - based on the calculated score, a patient's IMF is categorized as "low", "intermediate 1", "intermediate 2", or "high" with a mean survival of 185, 78, 35, and 16 mo, respectively
- risk of transformation to AML (8-10%)

**A Double-Blind, Placebo-Controlled Trial of Ruxolitinib for Myelofibrosis**
NEJM 2012;366:799-807
**Study**: Double-blinded RCT of 309 patients with myelofibrosis randomized to ruxolitinib or placebo.
**Outcome**: Primary outcome was reduction in spleen volume of >35% at 24 wk. Secondary outcomes were durability of response, symptom burden, and overall survival.
**Results**: A greater proportion of patients on ruxolitinib had reduction in spleen volume >35% (41.9% vs. 0.7%) and this was sustained in 67% at 48 wk. Ruxolitinib also led to greater symptom improvement (45% vs. 5.3%) and less mortality (13 vs. 24). There was no difference in rate of discontinuation due to adverse events (11.0% vs. 10.6%) but anemia and thrombocytopenia were more common with ruxolitinib.
**Conclusions**: Ruxolitinib reduced spleen size, improved symptoms and improved survival, compared with placebo.

## Essential Thrombocythemia

### Definition
- overproduction of platelets in the absence of recognizable stimulus
- must rule out secondary thrombocythemia

### Epidemiology
- increases with age; F:M = 2:1, but F=M at older age

### Diagnosis (2008 WHO Criteria Revised in 2016) requires meeting all four criteria
1. sustained platelet count >450 x $10^9$/L
2. bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased number of enlarged, mature megakaryocytes; no significant increase or left shift of neutrophil granulopoiesis or erythropoiesis
3. not meeting WHO criteria for PV, primary myelofibrosis, bcr-abl CML, or myelodysplastic syndrome or other myeloid neoplasms
4. demonstration of JAK2 V617F, calreticulin or MPL mutation (or in its absence another clonal marker), no evidence for reactive thrombocytosis

### Clinical Features
- often asymptomatic
- vasomotor symptoms (40%)
  - headache (common), dizziness, syncope
  - erythromelalgia (burning pain of hands and feet, dusky colour, usually worse with heat, caused by platelet activation → microvascular thrombosis)
- thrombosis (arterial and venous)
- bleeding (often GI; associated with platelets >1000 x $10^9$/L)
- constitutional symptoms, splenomegaly
- pregnancy complications; increased risk of spontaneous abortion
- risk of transformation to AML (0.6-5%), myelofibrosis

### Investigations
- CBC: increased platelets; may have abnormal platelet aggregation studies or vWD studies
- JAK2 PCR assay; if negative, CALR PCR assay
- bone marrow hypercellularity, megakaryocytic hyperplasia, giant megakaryocytes
- increased $K^+$, increased $PO_4^{3-}$ (2º to release of platelet cytoplasmic contents)
- diagnosis: exclude other myeloproliferative disorders and reactive thrombocytosis

### Treatment
- low dose ASA if previous history of thrombotic event, ≥1 cardiovascular risk factors, older, or symptomatic
- cytoreductive therapy if thrombosis or thrombotic symptoms: hydroxyurea (HU) (1st-line therapy), anagrelide, interferon-α, or 32P (age >80 or lifespan <10 yr)

**Etiology of Secondary Thrombocythemia**
- Infection
- Inflammation (IBD, arthritis)
- Malignancy
- Hemorrhage
- Iron deficiency
- Hemolytic anemia
- Post splenectomy
- Post chemotherapy

**Anagrelide vs. Hydroxyurea for Essential Thrombocythemia: ANAHYDRET Study, A Randomized Controlled Trial**
Blood 2013;121:1720-8
**Study**: Prospective, non-inferiority, RCT. Majority of patients followed beyond 1 yr.
**Population**: 259 previously untreated, high-risk patients with essential thrombosis as per the WHO guidelines.
**Intervention**: Patients were randomized to receive either non-immediate release formulation of anagrelide or hydroxyurea.
**Outcome**: Examined platelet counts, hemoglobin levels, leukocyte counts, and occurrence of ET-related events.
**Results**: The hazard ratio (HR) of developing thrombocythemia was 1.19 (95% CI 0.61-2.30). The HR for a reduction of hemoglobin was 1.03 (95% CI 0.57-1.81), and 0.92 (95% CI 0.57-1.46) for leukocytosis. There was no statistical difference in occurrence of major or minor arterial or venous thrombosis, severe or minor bleeding events, or rate of discontinuation between the two arms.
**Conclusions**: In patients with ET, anagrelide is non-inferior to hydroxyurea in the prevention of thrombotic complications.

There is an asymptomatic "benign" form of essential thrombocythemia with a stable or slowly rising platelet count; treatment includes observation, ASA, sulfinpyrazone, or dipyridamole

# Lymphoid Malignancies

## Acute Lymphoblastic Leukemia

### Definition

- malignant disease of the bone marrow in which early lymphoid precursors proliferate and replace the normal hematopoietic cells of the marrow
- WHO subdivides ALL into two types depending on cell of origin
  - 1. B-cell: precursor B lymphoblastic leukemia
  - 2. T-cell: precursor T lymphoblastic leukemia
- the French-American-British (FAB) classification (L1, L2, L3) is no longer encouraged, as morphology is not prognostic

75% of ALL occurs in children <6 yr old; second peak at age 40

### Clinical Features

- see *Acute Myeloid Leukemia*, H38 for full list of symptoms
- distinguish ALL from AML based on Table 32
- clinical symptoms usually secondary to:
  - bone marrow failure: anemia, neutropenia (50% present with fever; also infections of oropharynx, lungs, perianal region), and thrombocytopenia
  - organ infiltration: tender bones, lymphadenopathy, hepatosplenomegaly, meningeal signs (headache, N/V, visual symptoms; especially in ALL relapse)

### Investigations

- CBC: increased leukocytes >10 x $10^9$/L (occurs in 50% of patients); neutropenia, anemia, or thrombocytopenia
- may have increased uric acid, $K^+$, $PO_4^{3-}$, $Ca^{2+}$, LDH
- PT, aPTT, fibrinogen, D-dimers for DIC
- leukemic lymphoblasts lack specific morphological (no granules) or cytochemical features, therefore diagnosis depends on immunophenotyping
- cytogenetics: Philadelphia (Ph) chromosome in ~25% of adult ALL cases
- CXR: patients with ALL may have a mediastinal mass
- LP prior to systemic chemotherapy to assess for CNS involvement (ensure adequate platelet count and PT/PTT)
- HIV, HepB, HepC serologies

### Treatment

- eliminate abnormal clonal cells
  1. induction chemotherapy: to induce complete remission (undetectable leukemic blasts, restore normal hematopoiesis)
  2. consolidation and/or intensification of chemotherapy
     - consolidation: continuing same chemotherapy to eliminate subclinical leukemic cells
     - intensification: high doses of different (non-cross-reactive) chemotherapy drugs to eliminate cells with resistance to primary treatment
  3. maintenance chemotherapy: low dose intermittent chemotherapy over prolonged period (2-3 yr) to prevent relapse
  4. prophylaxis: CNS radiation therapy or methotrexate (intrathecal or systemic)
- hematopoietic stem cell transplantation: potentially curative (due to pre-implant myeloablative chemoradiation and post-implant graft-versus-leukemia effect) but relapse rates and non-relapse mortality high

**Treatment of ALL vs. AML**
- No proven benefit of maintenance chemotherapy in AML
- No routine CNS prophylaxis in AML

### Prognosis

- depends on response to initial induction or if remission is achieved following relapse
- good prognostic factors: young, WBC <30 x $10^9$/L, T-cell phenotype, absence of Ph chromosome, early attainment of complete remission
- achievement of first remission: 60-90%
- childhood ALL: 75% long-term remission (>5 yr)
  - higher cure rates in children because of better chemotherapy tolerance, lower prevalence of BCR-Abl fusion gene (associated with chemotherapeutic resistance)
- adult ALL: 30-40% 5 yr survival

**Table 32. Differentiating AML From ALL**

| AML | ALL |
|---|---|
| Big people (adults) | Small people (kids) |
| Big blasts | Small blasts |
| Big mortality rate | Small mortality rate (kids) |
| Lots of cytoplasm | Less cytoplasm |
| Lots of nucleoli (3-5) | Few nucleoli (1-3) |
| Lots of granules and Auer rods | No granules |
| Myeloperoxidase, Sudan black stain | PAS (periodic acid-Schiff) |
| Maturation defect beyond myeloblast or promyelocyte | Maturation defect beyond lymphoblast |

**To Differentiate AML from ALL:**
Remember **Big** and Sm**ALL**

# Lymphomas

## Definition

- collection of lymphoid malignancies in which malignant lymphocytes accumulate at lymph nodes and lymphoid tissues
  - leading to lymphadenopathy, extranodal disease, and constitutional symptoms

**American Society of Hematology Choosing Wisely Recommendation**
Limit surveillance CT scans in asymptomatic patients after curative-intent treatment for aggressive lymphoma

**Table 33. Ann Arbor System for Staging Lymphomas**

| Stage | Description |
|---|---|
| I | Involvement of a single lymph node region OR extralymphatic organ/site (Stage IE) |
| II | Involvement of two or more lymph node regions or an extralymphatic site and one or more lymph node regions on same side of diaphragm |
| III | Involvement of lymph node regions on both sides of the diaphragm; may or may not be accompanied by single extra lymphatic site or splenic involvement |
| IV | Diffuse involvement of one or more extralymphatic organs including bone marrow |

- Ann Arbor staging can be used for both Hodgkin and non-Hodgkin lymphoma, but grade/histology is more important for non-Hodgkin lymphoma because the outcome differs significantly depending on type of lymphoma
- Prognostic scores are different for indolent versus aggressive lymphomas
- Highly aggressive lymphomas act like acute leukemias

- subtypes
  - A = absence of B-symptoms (see *Approach to Lymphadenopathy*, H12)
  - B = presence of B-symptoms

**Table 34. Chromosome Translocations**

| Translocation | Gene Activation | Associated Neoplasm |
|---|---|---|
| t(2;5) | ALK1 mutation | Anaplastic large cell lymphoma |
| t(8;14) | c-Myc activation | Burkitt's lymphoma |
| t(14;18) | Bcl-2 activation | Follicular lymphoma |
| t(11;14) | Overexpression of cyclin D1 protein | Mantle cell lymphoma |
| t(11;18) | MALT1 activation | Mucosa-associated lymphoid tissue (MALT) |

# Hodgkin Lymphoma

## Definition

- malignant proliferation of lymphoid cells with Reed-Sternberg cells (thought to arise from germinal centre B-cells)

Hodgkin is distinguished from non-Hodgkin lymphoma by the presence of Reed-Sternberg cells

## Epidemiology

- bimodal distribution with peaks at 20 yr and >50 yr
- association with Epstein-Barr virus in up to 50% of cases and causal role not determined

## Clinical Features

- asymptomatic lymphadenopathy (70%)
  - non-tender, rubbery consistency
  - cervical/supraclavicular (60-80%), axillary (10-20%), inguinal (6-12%)
- splenomegaly (50%) ± hepatomegaly
- mediastinal mass
  - found on routine CXR, may be symptomatic (cough)
  - rarely may present with superior vena cava syndrome and pleural effusion
- systemic symptoms
  - B symptoms (especially in widespread disease; fever in 30%, night sweats, weight loss) and pruritus
- non-specific/paraneoplastic
  - alcohol-induced pain in nodes and nephrotic syndrome
- starts at a single site in lymphatic system (node) and spreads first to adjacent nodes
  - disease progresses in contiguity with lymphatic system

Hodgkin lymphoma classically presents as a painless, non-tender, firm, rubbery enlargement of superficial lymph nodes, most often in the cervical region

## Investigations

- CBC
  - anemia (chronic disease, rarely hemolytic), eosinophilia, lymphopenia, platelets normal or increased early disease, and decreased in advanced disease
- biochemistry
  - HIV, HepB, HepC serologies
  - liver enzymes and/or LFTs (liver involvement)
  - renal function tests (prior to initiating chemotherapy)
  - ALP, $Ca^{2+}$ (bone involvement)
  - ESR, LDH (monitor disease progression)
- imaging
  - CXR, CT chest (lymph nodes, mediastinal mass), CT abdomen/pelvis (liver or spleen involvement), and PET scans

  - cardiac function assessment (MUGA scan or echocardiography): for patients at high risk of pre-treatment cardiac disease (age >60, history of HTN, CHF, PUD, CAD, MI, CVA, and malnourished), treatment can be cardiotoxic
  - PFTs: if history of lung disease (COPD, smoking, and previous radiation to lung)
- excisional lymph node or core biopsy confirms diagnosis
- bone marrow biopsy to assess marrow infiltration (only necessary if B-symptoms, PET positive marrow on imaging, or cytopenia)

### Treatment

- stage I-II: chemotherapy (ABVD) followed by involved field or involved site radiotherapy (XRT)
- stage III-IV: chemotherapy (ABVD) with XRT for bulky disease
- relapse, resistant to therapy: high dose chemotherapy and autologous stem cell transplant
  - PET scan results essential in clarifying disease response

Treatment of HL depends on stage; treatment of NHL depends on histologic subtype

### Complications of Treatment

- cardiac disease: secondary to XRT, adriamycin is also cardiotoxic
- pulmonary disease: secondary to bleomycin (interstitial pneumonitis)
- infertility: recommend sperm banking
- secondary malignancy in irradiated field
  - <2% risk of MDS, AML (secondary to treatment, usually within 8 yr)
  - solid tumours of lung, breast; >8 yr after treatment
  - non-Hodgkin lymphoma
- hypothyroidism: post XRT

### Prognosis

- Hasenclever adverse prognostic factors:
  1. serum albumin <40 g/L
  2. hemoglobin <105 g/L
  3. male
  4. stage IV disease
  5. age ≥45 yr
  6. leukocytosis (WBC >1.5 x $10^9$/L)
  7. lymphocytopenia (lymphocytes <0.06 x $10^9$/L or <8% of WBC count or both)
- prognostic score
  - each additional adverse prognostic factor decreases freedom from progression at 5 yr (FFP)

**International Prognostic Factors Project 1998**

| Prognostic Factors | FFP |
|---|---|
| 0 | 84% |
| 1 | 77% |
| 2 | 67% |
| 3 | 60% |
| 4 | 51% |
| 5-7 | 42% |

FFP = freedom from progression at 5 yr

## Non-Hodgkin Lymphoma

### Definition

- malignant proliferation of lymphoid cells of progenitor or mature B- or T-cells

### Classification

- multiple classification systems exist at present and may be used at different centres
- can originate from both B- (85%) and T- or NK- (15%) cells
  - B-cell NHL: e.g. diffuse large B-cell lymphoma, follicular lymphoma, Burkitt's lymphoma, and mantle cell lymphoma
    - WHO/REAL classification system: 3 categories of NHLs based on natural history
    - indolent (35-40% of NHL): e.g. follicular lymphoma, small lymphocytic lymphoma/CLL, and mantle cell lymphoma
    - aggressive (~50% of NHL): e.g. diffuse large B-cell lymphoma
    - highly aggressive (~5% of NHL): e.g. Burkitt's lymphoma
  - T-cell NHL: e.g. mycosis fungoides (skin), TCL-NOS, and anaplastic large cell lymphoma

### Clinical Features

- painless superficial lymphadenopathy, usually >1 lymph node region
- usually presents as widespread disease (exception is aggressive lymphoma)
- constitutional symptoms not as common as in Hodgkin lymphoma
- cytopenia: anemia ± neutropenia ± thrombocytopenia can occur when bone marrow is involved
- abdominal signs ± hepatosplenomegaly, retroperitoneal and mesenteric involvement (second most common site of involvement)
- oropharyngeal involvement in 5-10% with sore throat and obstructive apnea
- extranodal involvement: most commonly GI tract; also testes, bone, and kidney
- CNS involvement in 1% (often with HIV)

**NHL: Associated Conditions**

- Immunodeficiency (e.g. HIV)
- Autoimmune diseases (e.g. SLE)
- Infections (e.g. EBV)

### Investigations

- CBC
  - normocytic normochromic anemia
  - autoimmune hemolytic anemia rare
  - advanced disease: thrombocytopenia, neutropenia, and leukoerythroblastic anemia
- peripheral blood film may show lymphoma cells
- flow cytometry of peripheral blood lymphocytosis is valuable for low-grade NHL

- biochemistries, HIV, HepB, HepC serologies
  - increase in uric acid
  - abnormal LFTs in liver metastases
  - increased LDH (rapidly progressing disease and poor prognostic factor)
- staging: CT neck, chest, abdomen, pelvis and bone marrow biopsy
- PET imaging must be done post therapy to ensure post treatment remission
- diagnosed by:
  - lymph node biopsy: excisional biopsy preferred, FNA unreliable
  - bone marrow biopsy: not optimal for diagnosis as BM involved in only 30% of high grade lymphomas

## Treatment

- localized disease (e.g. GI, brain, bone, head and neck)
  - radiotherapy to primary site and adjacent nodal areas
  - adjuvant chemotherapy
  - surgery: splenic marginal zone lymphoma
- indolent lymphoma: goal of treatment is symptom management
  - watchful waiting
  - radiation therapy for localized disease
  - bendamustine plus rituximab, an anti-CD20 antibody, is superior to CHOP and rituximab (CHOP-R) for advanced stage disease (StIL trial)
  - obinutuzumab superior to rituximab for advanced stage follicular lymphoma (GALLIUM Trial)
- aggressive lymphoma: goal of treatment is curative
  - combination chemotherapy: CHOP is mainstay, plus rituximab if B-cell lymphoma
  - radiation for localized/bulky disease
  - CNS prophylaxis with high-dose methotrexate if certain sites involved (testicular)
  - relapse, resistant to therapy: high dose chemotherapy, autologous SCT
- highly aggressive lymphoma
  - Burkitt lymphoma: short bursts of intensive chemotherapy "CODOX-M" chemotherapy regimen also often used ± IVAC with Rituximab
  - CNS prophylaxis and tumour lysis syndrome prophylaxis

**Common Chemotherapeutic Regimens**
**CHOP:** cyclophosphamide, hydroxydoxorubicin (Adriamycin®), vincristine (Oncovin®), prednisone
**VAD:** vincristine, adriamycin, dexamethasone
**ABVD:** adriamycin, bleomycin, vinblastine, dacarbazine
**BEACOPP:** bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone

## Complications

- hypersplenism
- infection
- autoimmune hemolytic anemia and thrombocytopenia
- vascular obstruction (from enlarged nodes)
- bowel perforation
- tumour lysis syndrome (particularly in very aggressive lymphoma) see *Tumour Lysis Syndrome*, H52

## Prognosis

- follicular lymphoma: Follicular Lymphoma International Prognostic Index is used (5 adverse prognostic factors): age >60; >4 nodal areas; elevated LDH; Lugano stage III-IV; hemoglobin <120 g/L
  - based on calculated risk, mean 5 yr survival ranges from 53-91%
  - rarely curative, typically relapsing and remitting course with risk of transformation to aggressive lymphoma such as diffuse large B-cell lymphoma
- diffuse large B-cell lymphoma: The International Prognostic Factor Index is used (5 adverse prognostic factors): age >60; Ann Arbor stage (III-IV); performance status (ECOG/Zubrand 2-4); elevated LDH; >1 extranodal site
  - based on calculated risk, mean 5 yr survival ranges from 26-73%
  - ~40% rate of cure

**Table 35. Characteristics of Select Non-Hodgkin Lymphomas**

| | Follicular Lymphoma | Diffuse Large B-Cell Lymphoma (DLBCL) | Burkitt Lymphoma | Mantle Cell Lymphoma |
|---|---|---|---|---|
| **Percentage of NHLs** | 22-30% | 33% | <1% adult NHLs<br>30% childhood NHLs | 6% |
| **Genetic Mutation** | Bcl-2 activation | Bcl-2, Bcl-6, Myc rearrangements | c-Myc activation | Overexpression of cyclin D1 (Bcl-1 activation) |
| **Classification** | Indolent | Aggressive (high-grade) | Very aggressive | Indolent |
| **Risk Factors** | Middle-age – elderly | Previous CLL (Richter's transformation: 5% CLL patients progress to DLBCL) | 1. Endemic: African origin, EBV-associated<br>2. Sporadic: no EBV<br>3. HIV-related: AIDS-defining illness | Male (M:F = 4:1) |
| **Clinical Features** | Widespread painless LAD* ± bone marrow involvement<br>Frequent transformation to aggressive lymphoma<br>Very responsive to chemoradiation treatment | Rapidly progressive LAD and extranodal infiltration<br>50% present at stage I/II, 50% widely disseminated | Endemic form: massive jaw LAD "Starry-sky" histology<br>High risk of tumour lysis syndrome upon treatment | Often presents Stage IV with palpable LAD<br>Involvement of GI tract (lymphomatosis polyposis), Waldeyer's Ring<br>5 yr survival 25% |

*LAD = lymphadenopathy

# Malignant Clonal Proliferations of Mature B-Cells

**Table 36. Characteristics of B-Cell Malignant Proliferation**

| | CLL | Lymphoplasmacytic Lymphoma | Myeloma |
|---|---|---|---|
| **Cell Type** | Lymphocyte | Plasmacytoid | Plasma cell |
| **Protein** | IgM if present | IgM | IgG, A, light chain (rarely M, D, or E) |
| **Lymph Nodes** | Very common | Common | Rare |
| **Hepatosplenomegaly** | Common | Common | Rare |
| **Bone Lesions** | Rare | Rare | Common |
| **Hypercalcemia** | Rare | Rare | Common |
| **Renal Failure** | Rare | Rare | Common |
| **Immunoglobulin Complications** | Common | Rare | Rare |



Rouleaux formation on peripheral blood smear, if not artifact, denotes hyperglobulinemia (but not necessarily monoclonality)

## Chronic Lymphocytic Leukemia




### Definition
- indolent disease characterized by clonal malignancy of mature B-cells

### Epidemiology
- most common leukemia in Western world
- mainly older patients; median age 70 yr
- M>F

### Pathophysiology
- accumulation of neoplastic lymphocytes in blood, bone marrow, lymph nodes, and spleen

### Clinical Features
- 25% asymptomatic (incidental finding)
- 5-10% present with B-symptoms (≥1 of: unintentional weight loss ≥10% of body weight within previous 6 mo, temperature >38°C, or night sweats for ≥2 wk without evidence of infection, extreme fatigue)
- lymphadenopathy (50-90%), splenomegaly (25-55%), hepatomegaly (15-25%)
- immune dysregulation: autoimmune hemolytic anemia (DAT positive), ITP, hypogammaglobulinemia ± neutropenia
- bone marrow failure: late, secondary to marrow involvement by CLL cells

### Investigations
- CBC: clonal population of B lymphocytes >5 x $10^9$/L
- peripheral blood film
  - lymphocytes are small and mature
  - smudge cells

characteristic flow cytometry of peripheral blood
  - CD5, CD20dim, CD23
- cytogenetics: FISH (dictates response to therapy and prognosis). imaging must be done post therapy to ensure post treatment remission v=
- bone marrow aspirate
  - lymphocytes >30% of all nucleated cells
  - infiltration of marrow by lymphocytes in 4 patterns: nodular (10%), interstitial (30%), diffuse (35%, worse prognosis), or mixed (25%)



Smudge cells are artifacts of damaged lymphocytes from slide preparation

### Natural History and Treatment
- natural history: indolent and incurable; most cases show slow progression
- small minority present with aggressive disease; usually associated with chromosomal abnormalities (e.g. p53 deletion)
- first line therapy is dictated by cytogenetic status and patient co-morbidities
  - observation if early, stable, asymptomatic
    - treatment options vary by region; commonly fludarabine + cyclophosphamide + rituximab (FCR) in fit patients with normal CrCl; bendamustine + rituximab (BR) in less fit
    - chlorambucil + anti-CD20 obinutuzumab in the elderly
    - Ibrutinib (BTK inhibitor) in patients with IgVH mutation negativity and/ p53 positivity
  - corticosteroids, IVIg: especially for autoimmune phenomena
  - radiotherapy for isolated bulky nodes
- molecular therapies
  - Idelalisib – PI3K inhibitor
  - Ibrutinib – BTK (Bruton's tyrosine kinase) inhibitor
  - Venetoclax – BCL-2 inhibitor

### Prognosis
- 9 yr median survival, but varies greatly
- prognosis predicted by Rai staging based on leukocytosis and cytogenetic status
- low risk: lymphocytosis in blood and bone marrow only
- intermediate risk: lymphocytosis with enlarged nodes in any site or splenomegaly, hepatomegaly
- high risk: lymphocytosis with disease-related anemia (<110 g/L) or thrombocytopenia (<100 x $10^9$/L)

### Complications
- bone marrow failure
- immune complications: AIHA, ITP, immune deficiency (hypogammaglobulinemia, and impaired T-cell function)
- polyclonal or monoclonal gammopathy (often IgM)
- hyperuricemia with treatment
- 5% undergo Richter's transformation: aggressive transformation to diffuse large B-cell lymphoma (see Table 35)

## Multiple Myeloma

### Definition
- neoplastic clonal proliferation of plasma cells producing a monoclonal immunoglobulin resulting in end organ dysfunction
- usually single clone of plasma cells, although biclonal myeloma also occurs; rarely non-secretory
- preceded by asymptomatic myeloma or MGUS

### Epidemiology
- incidence 3 per 100,000, most common plasma cell malignancy
- increased frequency with age; median age of diagnosis is 68 yr; M>F

### Pathophysiology
- malignant plasma cells secrete monoclonal antibody
  - 95% produce M protein (monoclonal Ig = identical heavy chain + identical light chain, or light chains only)
    - IgG 50%, IgA 20%, IgD 2%, IgM 0.5%
    - 15-20% produce free light chains or light chains alone found in either:
      - serum as an increase in the quantity of either kappa or lambda light chain (with an abnormal kappa:lambda ratio)
      - urine has Bence-Jones protein
  - <5% are non-secretors

### Clinical Features and Complications
- bone disease: pain (usually back), bony tenderness, pathologic fractures
  - lytic lesions are classical (skull, spine, proximal long bones, ribs)
  - increased bone resorption secondary to osteoclast activating factors such as PTHrP
- anemia: weakness, fatigue, pallor
  - secondary to bone marrow suppression
- weight loss
- infections
  - usually *S. pneumoniae* and Gram-negatives
  - secondary to suppression of normal plasma cell function
- hypercalcemia: N/V, confusion, constipation, polyuria, and polydipsia
  - secondary to increased bone turnover
- renal disease/renal failure
  - most frequently causes cast nephropathy (see Nephrology, NP33)
- bleeding
  - secondary to thrombocytopenia, may see petechiae, purpura
  - can also be caused by acquired von Willebrand disease
- extramedullary plasmacytoma
  - soft tissue mass composed of monoclonal plasma cells, purplish colour
- hyperviscosity: may manifest as headaches, stroke, angina, and MI
  - rare in MM as secondary to increased viscosity caused by IgM protein (more common in WM/ LPL)
- amyloidosis
  - accumulation of insoluble fibrillar protein (Ig light chain) in tissues; can cause infiltration of any organ system: cardiac infiltration – diastolic dysfunction, cardiac arrhythmias, syncope, sudden death; GI involvement – malabsorption, beefy large or laterally scalloped tongue; neurologic involvement – orthostatic hypotension, carpal tunnel syndrome
  - may cause Factor X deficiency if fibrils bind Factor X → bleeding (raccoon eyes)
- neurologic disease: muscle weakness, pain, and paresthesias
  - radiculopathy caused by vertebral fracture and extramedullary plasmacytoma
  - spinal cord compression (10-20% of patients) is a medical emergency





**Multiple Myeloma**
**SLiM CRAB**
**S**ixty percent plasma cells in bone marrow specimen
**L**ight chain ratio >100
**M**RI lytic lesion >0.5 cm
**C**alcium >2.80 mmol/L
**R**enal failure (Cr >176 mmol/L)
**A**nemia
**B**ony lesions (lytic lesions or osteoporosis felt to be caused by myeloma)



**Amyloid**
The general term for a variety of proteinaceous materials that have a similar structural organization and are abnormally deposited in tissues

Found in a variety of clinical disorders and can cause systemic (e.g. MM [light chains]) or localized amyloidosis (e.g. Alzheimer disease [AB amyloid])

## Investigations

- CBC
  - normocytic anemia, thrombocytopenia, and leukopenia
  - rouleaux formation on peripheral film
- biochemistry
  - increased $Ca^{2+}$, increased ESR, decreased anion gap, increased Cr, albumin, β2-microglobulin (as part of staging), and proteinuria (24 h urine collection)
- monoclonal proteins
  - serum protein electrophoresis (SPEP): demonstrates monoclonal protein spike in serum in 80% (i.e. M protein)
  - urine protein electrophoresis (UPEP): demonstrates light chains in urine = Bence-Jones protein (15% secrete only light chains)
  - immunofixation: demonstrates M protein and identifies Ig type; also identifies light chains
  - serum free light chain quantification: kappa and lambda light chains, calculated ratio
- bone marrow aspirate and biopsy
  - often focal abnormality, greater than 10% plasma cells, abnormal morphology, clonal plasma cells; send for fluorescence *in situ* hybridization (FISH) or cytogenetics (prognostic implications)
- skeletal series (X-rays), MRI if symptoms of cord compression
  - presence of lytic lesions and areas at risk of pathologic fracture
  - bone scans are not useful since they detect osteoblast activity
- β2-microglobulin, LDH, and CRP are poor prognosticators
  - HepBsAb, HepBsAg, HepBcAb

Routine urinalysis will not detect light chains as dipstick detects albumin. Need sulfosalicylic acid or 24 h urine protein for immunofixation or electrophoresis

**Light Chain Disease**
15% of MM produce only light chains
Renal failure is a major problem
Kappa > lambda light chain has better prognosis

## Diagnosis

- International Myeloma Working Group Criteria ("SLiM CRAB"):
  - Sixty (60) percent or greater abnormal plasma cells on bone marrow examination
  - Light chain ratio (free, involved/uninvolved) of 100 or more in the blood (involved must be at least 100 mg/L)
  - MRI with more than one bone lesion (5 mm or greater)
  - CRAB – presence of end-organ damage related to plasma cell dyscrasia, such as:
    - increased serum $Ca^{2+}$
    - renal failure
    - anemia
    - lytic bone lesions

## Treatment

- non-curative
- treatment goals
  - improvement in quality of life (improve anemia, reverse renal failure, prevent fractures)
  - prevention of progression and complications
  - increase overall survival
- autologous stem cell transplant if <65 yr old
  - usually preceded by 4-6 mo of cytoreductive therapy: steroid based with novel agents (i.e. immunomodulatory drugs - IMIDs or proteasome inhibitors - PI)
- chemotherapy if >65 yr old or transplant-ineligible
  - pending on patient co-morbidities can include a combination of: melphalan, prednisone, cyclophosphamide, PI (i.e. bortezomib), IMIDs, anti-CD38 agents (e.g. daratumumab)
- dexamethasone and bortezomib if ARF; bortezomib ± dexamethasone in light chain amyloidosis
- supportive management
  - bisphosphonates for those with osteopenia or lytic bone lesions (requires renal dosing)
  - local XRT for bone pain, spinal cord compression
  - kyphoplasty for vertebral fractures to improve pain relief and regain height
  - treat complications: hydration for hypercalcemia and renal failure, bisphosphonates for severe hypercalcemia, prophylactic antibiotics, erythropoietin for anemia, and DVT prophylaxis
- all patients will relapse; choice of retreatment regimen depends on duration of remission, organ involvement, patient's comorbidities, and preferences

**Serum Free Light Chain Ratio is an Independent Risk Factor for Progression in MGUS**
Blood 2005;106:812-817
**Purpose**: To determine whether the presence of monoclonal free kappa or lambda immunoglobulin light chains in MGUS increases the risk of progression to malignancy.
**Methods**: Retrospective study with median follow-up of 15 yr. Baseline serum samples obtained from 1383 MGUS patients seen at the Mayo clinic between 1960-1994. 1148 baseline samples were obtained within 30 d of diagnosis.
**Results**: Malignant progression had occurred in 87 (7.6%) patients. In 379 (33%) patients, an abnormal serum free light chain (FLC) ratio was detected. There was a significantly higher risk of progression in patients with an abnormal FLC ratio relative to patients with a normal ratio (hazard ratio, 3.5; 95% CI 2.3-5.5; p<0.001). This finding was independent of the size and type of the serum monoclonal (M) protein. In high-risk MGUS patients (abnormal serum FLC ratio, non-IgG MGUS, high serum M protein level [≥1.5 gm/dL]), the risk of progression at 20 yr was 58% compared to 37% in high-intermediate-risk MGUS (two risk factors), 21% low-intermediate risk (with one risk factor) and 5% low-risk (no risk factors).
**Conclusions**: The presence of an abnormal FLC ratio is a clinically and statistically significant predictor of progression in MGUS. The low-risk subset of patients with MGUS accounts for 40% of all MGUS patients and have a small lifetime risk of progression, thus less follow-up can be justified.

## Prognosis

- ISS - International Staging System (β2-microglobulin and albumin) used to stage and estimate prognosis
- revised ISS for risk stratification: combination of original ISS, cytogenetic profile (i.e. p53 mutation associated with poor survival and resistance to chemotherapy), and LDH
- median survival based on stage, usually 3-7 yr

# Monoclonal Gammopathy of Unknown Significance

### Definition
- presence of M protein in serum in absence of any clinical or laboratory evidence of a plasma cell dyscrasia or lymphoproliferative disorders
  - incidence: 0.15% in general population, 5% of people >70 yr of age
  - asymptomatic

### Diagnosis
- presence of a serum monoclonal protein (M protein) at a concentration <30 g/L
- <10% plasma cells in bone marrow
- absence of SLiM CRAB
- 0.3-1% of patients develop a hematologic malignancy each yr
  - patients with M protein peak ≥15 g/L or patients with IgA or IgM MGUS are at higher risk of malignant transformation
  - patients with abnormal serum free light chains ratio are at increased risk of malignant transformation
- monitor with annual history, physical, CBC, Cr, calcium, albumin, and serum protein electrophoresis (considered pre-malignant)
- all patients must have skeletal imaging at diagnosis (typically skeletal survey ± MRI spine as per symptoms)

# Waldenstrom's Macroglobulinemia (WM)

### Definition
- WM aka Lymphoplasmacytic Lymphoma (LPL)
- proliferation of lymphoplasmacytoid cells
  - presence of monoclonal IgM paraprotein



Waldenstrom's macroglobulinemia accounts for 85% of all cases of hyperviscosity syndrome

### Clinical Features
- chronic disorder of elderly patients; median age 64 yr
- symptoms: weakness, fatigue, bleeding (oronasal), weight loss, recurrent infections, dyspnea, CHF (triad of anemia, hyperviscosity, plasma volume expansion), neurological symptoms, peripheral neuropathy, and cerebral dysfunction
- signs: pallor, splenomegaly, hepatomegaly, lymphadenopathy, and retinal lesions
- key complication to avoid: hyperviscosity syndrome
  - because IgM (unlike IgG) confined largely to intravascular space

### Investigations and Diagnosis
- bone marrow shows plasmacytoid lymphocytes
- bone lesions usually not present
- blood work rarely shows hypercalcemia
- cold hemagglutinin disease possible: Raynaud's phenomenon, hemolytic anemia precipitated by cold weather
- normocytic anemia, rouleaux, and high ESR if hyperviscosity not present
- HepB, HepC serologies (NOTE: can be associated with HepC; HepC eradication can put LPL into remission)

### Treatment
- Bendamustine – R/R-CVP chemotherapy, alkylating agents (chlorambucil), nucleoside analogues (fludarabine), rituximab, or combination therapy
- if HepC positive – treat HepC prior to a trial of chemotherapy
- corticosteroids
- plasmapheresis for hyperviscosity: acute reduction in serum IgM

# Complications of Hematologic Malignancies

## Hyperviscosity Syndrome

### Definition
- refers to clinical sequelae of increased blood viscosity (when relative serum viscosity >5-6 units), resulting from increased circulating serum Igs or from increased cellular blood components in hyperproliferative disorders (e.g. multiple myeloma, leukemia, PV)
- Waldenstrom's macroglobulinemia accounts for 85% of cases

### Clinical Features
- hypervolemia causing: CHF, headache, lethargy, dilutional anemia
- CNS symptoms due to decreased cerebral blood flow: headache, vertigo, ataxia, and stroke
- retina shows venous engorgement and hemorrhages
- bleeding diathesis
  - due to impaired platelet function, absorption of soluble coagulation factors (e.g. nasal bleeding, oozing gums)
- ESR usually very low

### Treatment
- plasmapheresis, chemotherapy

# Tumour Lysis Syndrome

### Definition
- group of metabolic complications that result from spontaneous or treatment-related breakdown of cancer cells
- more common in diseases with large tumour burden and high proliferative rate (high grade lymphoma, leukemia)

### Clinical Features
- metabolic abnormalities
  - cells lyse, releasing $K^+$, uric acid, $PO_4^{3-}$ (increased levels)
  - $PO_4^{3-}$ binds $Ca^{2+}$ (decreased $Ca^{2+}$)
- complications
  - lethal cardiac arrhythmia (increased $K^+$)
  - acute kidney injury (formerly known as renal failure) see Nephrology, NP19

### Treatment
- prevention
  - aggressive IV hydration
  - alkalinization not recommended due to risk of calcium phosphate or xanthine precipitation in renal tubules
  - allopurinol or rasburicase
  - correction of pre-existing metabolic abnormalities
- dialysis

# Blood Products and Transfusions

### Blood Products
- RBCs, platelets and coagulation factors (frozen plasma [FP], cryoprecipitate, factor concentrates) are available for transfusion
- donated blood (1 U = 450-500 mL) is fractionated into these various components
  - centrifugation separates whole blood into RBCs and platelet-rich plasma
  - platelet-rich plasma is further fractionated into platelets and plasma
    - need to pool together multiple units to obtain therapeutic amounts
    - FP (previously known as FFP) is plasma frozen within 24 h of collection
    - cryoprecipitate is the high MW precipitate generated when FP is thawed at low temperatures

**Blood Groups**

| Group | Antigen (on RBC) | Antibody (in serum) |
|---|---|---|
| O | H | Anti-A, anti-B |
| A | A | Anti-B |
| B | B | Anti-A |
| AB | A and B | Nil |

### Specialized Products
- irradiated blood products
  - prevent proliferation of donor T-cells in potential or actual bone marrow transplant recipients
  - used for immunocompromised patients or for patients on purine analogue chemotherapy, first-degree relatives, HLA-matched products and intrauterine transfusions, Hodgkin lymphoma
- CMV-negative blood products
  - potential transplant recipients
  - neonates
  - AIDS patients
  - seronegative pregnant women

In Canada, blood products are leukodepleted via filtration immediately after donation; therefore it is considered:
- Low in lymphokines, resulting in a lower incidence of febrile nonhemolytic transfusion reactions
- CMV negative (because CMV is found in leukocytes)

# Red Blood Cells

### Packed Red Blood Cells
- stored at 4°C
- transfuse within 42 d of collection, otherwise cell lysis may result in hyperkalemia
- infuse each unit over 2 h (max of 4 h)

1 unit of pRBC will increase Hb by approximately 10 g/L or increase Hct by 4%

### Indications for Packed RBC Transfusion
- Hb <70 g/L; this may change as per patient's tolerance or symptoms
  - maintain Hb between 70 and 100 g/L during active bleeds
- consider maintaining a higher Hb for patients with:
  - CAD/unstable coronary syndromes
  - uncontrolled, unpredictable bleeding
  - impaired pulmonary function
  - increased $O_2$ consumption

**American Society of Hematology Choosing Wisely Recommendation**
Do not transfuse more than the minimum number of RBC units necessary to relieve symptoms of anemia or to return the patient to a safe hemoglobin range (70-80 g/L) in stable non-cardiac patients

### Selection of Red Cells for Transfusion

- when anticipating an RBC transfusion, the following should be ordered:
  - group and screen: determines the blood group and Rh status of the recipient as well as the presence of autoantibodies vs. major/minor blood group antigens in the patient's serum
  - cross-match: involves mixing the recipient's blood with potential donor blood and looking for agglutination (takes 30-45 min)
- when blood is required, several options are available
  - 1st-line: fully crossmatched blood, electronic crossmatch is becoming more widely used (not always available in emergency situations)
  - 2nd-line: donor blood of the same group and Rh status as the recipient
  - 3rd-line: O- blood for females of reproductive age; O+ blood for all others

# Platelets

**Table 37. Platelet Products**

| Product | Indication |
|---|---|
| **Random Donor (Pooled)** | Thrombocytopenia with bleeding |
| **Single Donor Platelets** | Potential BMT recipients. Refractory to pooled platelets. |
| **HLA Matched Platelets** | Refractory to pooled or single donor platelets, presence of HLA antibodies |

- stored at 20-24°C
- random donor platelets are transfused from a pool of 4 units; this should increase the platelet count by ≥15 x $10^9$/L
- single donor platelets (transfused as single units) should increase the platelet count by 40-60 x $10^9$/L
- if an increase in the platelet count is not seen post-transfusion: autoantibodies (i.e. ITP), alloantibodies, consumption (bleeding, sepsis), or hypersplenism may be present

**Table 38. Indications for Platelet Transfusion**

| Plt (x $10^9$/L) | Indications |
|---|---|
| **<10** | Non-immune thrombocytopenia |
| **<20** | Procedures not associated with significant blood loss |
| **<50** | Procedures associated with blood loss or major surgery (>500 mL EBL) |
| **<100** | Pre-neurosurgery or head trauma |
| **Any** | Platelet dysfunction (or antiplatelet agents) and marked bleeding |

### Relative Contraindications of Platelet Transfusion

- TTP, HIT, post-transfusion purpura, and HELLP

# Coagulation Factors

**Table 39. Coagulation Factor Products**

| Product | Indication |
|---|---|
| Frozen plasma (FP) | Depletion of multiple coagulation factors (e.g. sepsis, DIC, dilution, TTP/HUS, liver disease), emergency reversal of life-threatening bleeding secondary to warfarin overdose |
| Cryoprecipitate (enriched fibrinogen, vWF, VIII, XIII) | Hemophilia A (Factor VIII deficiency) – use in emergencies<br>von Willebrand disease – use in emergencies<br>Hypofibrinogenemia |
| Humate P or Wilate | von Willebrand disease<br>Hemophilia A |
| Factor VIII concentrate | Factor VIII deficiency (Hemophilia A) |
| Factor IX concentrate | Factor IX deficiency (Hemophilia B) |
| Recombinant factor VIIa | Factor VII deficiency with bleeding/surgery, Hemophilia A or B with inhibitors, Glanzmann thrombasthenia |
| Prothrombin complex concentrate; PCC (Octaplex®, Beriplex®) | Reversal of warfarin therapy or vitamin K deficiency in bleeding patient or in patient requiring urgent (<6 h) surgical procedure, urgent non-specific "reversal" of direct Xa inhibitors |
| Activated prothrombin complex concentrate; aPCC (FEIBA) | Hemophilia A or B with inhibitors, urgent non-specific "reversal" of direct thrombin inhibitors |



**Transfusion Requirements in Critical Care (TRICC)**
NEJM 1999;340:409-417
**Study**: Multicentre, RCT.
**Participants**: 838 critically ill patients with euvolemia after initial treatment and hemoglobin less than 9 g/dL within 72 h of ICU admission.
**Intervention**: Patients receiving a transfusion followed either (1) a restrictive strategy (RS; n=418) in which red cells were transfused if hemoglobin was less than 7.0 g/dL and then maintained at 7 to 9 g/dL) or (2) a liberal strategy (LS; n=420) in which transfusions occurred when the hemoglobin was less than 10.0 g/dL and then maintained at 10 to 12 g/dL.
**Primary Outcome**: Mortality at 30 d and severity of organ dysfunction.
**Results**: Mortality rates at 30 d were similar between groups. However, mortality rates were significantly lower with the RS among less acutely ill patients (8.7% and RS group and 16.1% in LS group; p=0.03) and among those <55 yr of age (5.7% RS and 13% LS; p=0.02), but did not differ in a subgroup with clinically significant cardiac disease.
**Conclusion**: A RS of red cell transfusion is at least as effective as, and possibly superior to, a LS transfusion in critically ill patients.



**Liberal or Restrictive Transfusion in High-Risk Patients After Hip Surgery (FOCUS)**
NEJM 2011;365:2453-2462
**Study**: Multicentre RCT.
**Participants**: 2016 patients aged greater than 50 yr with a history of or risk factors for cardiovascular disease and hemoglobin (Hb) level below 10 g/dL after hip-fracture surgery.
**Intervention**: Patients were randomly assigned to a liberal transfusion strategy (a Hb threshold of 10 g/dL) or a restrictive transfusion strategy (anemia symptoms or at physician discretion for a Hb level less than 8 g/dL).
**Primary Outcome**: Mortality or inability to walk across a room without human assistance on a 60 d follow-up.
**Results**: Primary outcome rates were 35.2% in the liberal transfusion strategy group and 34.7% in the restrictive transfusion strategy group. Rates of complications were similar in the two groups.
**Conclusion**: A liberal transfusion strategy did not reduce mortality rates or the inability to walk independently on 60 d follow-up compared to a restrictive transfusion strategy in elderly patients with high cardiovascular risk factors after hip surgery.



**Group & Screen vs Cross-Matching:**
G&S: ABO Group + Rh factor
Cross-Matching: match recipient's serum with donor's packed RBC or antibodies

# Acute Blood Transfusion Reactions

## IMMUNE

### Acute Hemolytic Transfusion Reactions
- ABO incompatibility resulting in intravascular hemolysis secondary to complement activation, occurs immediately after transfusion
- most commonly due to incorrect patient identification
- risk per unit of blood is <1 in 40,000
- presentation: fever, chills, hypotension, back or flank pain, dyspnea, hemoglobinuria
- acute renal failure (<24 h) and DIC
- treatment
  - stop transfusion
  - notify blood bank and check for clerical error
  - maintain BP with vigorous IV fluids ± inotropes
  - maintain urine output with diuretics, crystalloids, dopamine

### Febrile Nonhemolytic Transfusion Reactions
- due to alloantibodies to WBC, platelets or other donor plasma antigens, and release of cytokines from blood product cells
- occurs within 0-6 h of transfusion
- risk per unit of blood is 1 in 100 (minor), 1 in 10,000 to 40,000 (severe)
- presents with fever ± rigors, facial flushing, headache, myalgia, hypotension
- treatment
  - rule out hemolytic reaction or infection
  - if temperature <38°C, continue with transfusion but decrease rate and give antipyretics
  - if temperature >38°C, stop transfusion, give antipyretics and anti-histamine

### Allergic Nonhemolytic Transfusion Reactions
- alloantibodies (IgE) to proteins in donor plasma result in mast cell activation and release of histamine
- occurs mainly in those with history of multiple transfusions or multiparous women
- risk per unit of blood is 1 in 100
- presents mainly as urticaria and occasionally with fever
- can present as anaphylactoid reaction with bronchospasm, laryngeal edema, and hypotension, but this occurs mainly in IgA deficient patients that have anti-IgA antibodies
- treatment
  - mild: slow transfusion rate and give diphenhydramine
  - moderate to severe: stop transfusion, give IV diphenydramine, steroids, epinephrine, IV fluids, and bronchodilators

### Transfusion-Related Acute Lung Injury
- new-onset acute lung injury that occurs during transfusion or within 6 h of transfusion completion
  - insidious, acute onset of pulmonary insufficiency
  - profound hypoxemia ($PaO_2/FiO_2$ <300 mmHg)
  - bilateral pulmonary edema on CXR
  - pulmonary artery wedge pressure <18 mmHg
  - no clinical evidence of left atrial hypertension
- pathogenesis uncertain; perhaps due to binding of donor antibodies to WBC of recipient and release of mediators that increase capillary permeability in the lungs
- typically occurs 2-4 h post transfusion and resolves in 24-72 h
- risk per unit of blood is 1 in 10,000
  - is currently the leading cause of transfusion-related morbidity and mortality
- treatment: supportive therapy (oxygen)
- inform blood bank; patient and donor testing will be arranged

## NONIMMUNE

### Transfusion-Associated Circulatory Overload
- due to impaired cardiac function and/or excessive rapid transfusion
- presentation: dyspnea, orthopnea, hypotension, tachycardia, crackles at base of lung, and increased venous pressure
- incidence: 1 in 700 and is becoming more common
- treatment: transfuse at lower rate, give diuretics and oxygen

### Bacterial Infection
- Gram-positive: *S. aureus, S. epidermidis, Bacillus cereus*
- Gram-negative: *Klebsiella, Serratia, Pseudomonas, Yersinia*
- overall risk is 1 in 100,000 for RBC and 1 in 10,000 for platelets
- never store blood >4 h after bag has left blood bank
- treatment: stop transfusion, blood cultures, IV antibiotics, fluids



**DDx of Post-Transfusion Fever**
- Acute hemolytic transfusion reaction
- Febrile non-hemolytic transfusion reaction
- Bacterial contamination
- Allergy

**DDx of Post-Transfusion Dyspnea**
- Transfusion-associated circulatory overload (TACO)
- Transfusion-related acute lung injury (TRALI)
- Allergy (bronchospasm/anaphylaxis)

### Hyperkalemia
- due to $K^+$ release from stored RBC
- risk increases with storage time and if blood is irradiated and risk decreases if given fresh blood
- occurs in 5% of massively transfused patients
- treatment: see Nephrology, NP13

### Citrate Toxicity
- occurs with massive transfusion in patients with liver disease – patients are unable to clear citrate from blood
- citrate binds to $Ca^{2+}$ and causes signs and symptoms of hypocalcemia
- treatment: IV calcium gluconate (10 mL for every 2 units of blood)

### Dilutional Coagulopathy
- occurs with massive transfusion (>10 units)
- pRBC contains no clotting factors, fibrinogen, cryoprecipitate, or platelets
- treatment: FP, cryoprecipitate, and platelets

## Delayed Blood Transfusion Reactions

### IMMUNE

### Delayed Hemolytic
- due to alloantibodies to minor antigens such as Rh, Kell, Duffy, and Kidd
- level of antibody at time of transfusion is too low to cause hemolysis; later the level of antibody increases due to secondary stimulus and causes extravascular hemolysis
- occurs 5-7 d after transfusion
- presentation: anemia and mild jaundice
- treatment: no specific treatment required; important to note for future transfusion
- N.B. serologic transfusion reactions are the development of alloantibodies in the absence of frank hemolysis

### Transfusion-Associated Graft Versus Host Disease
- transfused T-lymphocytes recognize and react against "host" (recipient)
- occurs 4-30 d following transfusion
- most patients already have severely impaired immune systems (e.g. Hodgkin lymphoma or leukemia)
- presentation: fever, diarrhea, liver function abnormalities, and pancytopenia
- can be prevented by giving irradiated blood products



**Allogeneic SCT GVHD**
To reduce risk of GVHD development after allogeneic SCT, administer Inhibitors of T-cell activation, including cyclosporin A or tacrolimus

### NONIMMUNE

### Iron Overload
- due to repeated transfusions over long period of time (e.g. β-thalassemia major)
- can cause secondary hemochromatosis
- treatment: iron chelators or phlebotomy if no longer requiring blood transfusion and not anemic

### Viral Infection Risk
- HBV 1 in 1.1 to 1.7 million
- HCV 1 in 5 to 7 million
- HIV 1 in 8 to 12 million
- Human T-lymphotropic virus (HTLV) 1 in 1 to 1.3 million
- other infections include EBV, CMV, WNV (West Nile virus)

# Common Medications

## Antiplatelet Therapy

• see Figure 12a, *Platelet activation cascade*, H26

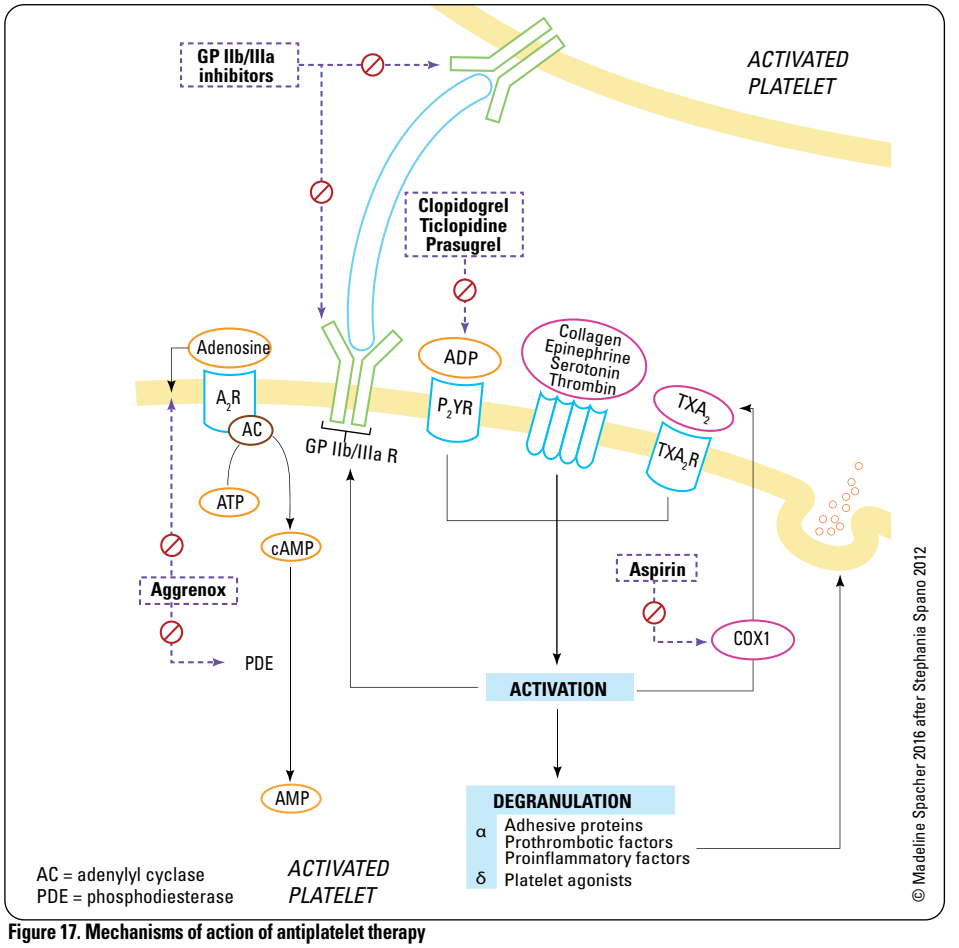



**Figure 17. Mechanisms of action of antiplatelet therapy**

**Table 40. Antiplatelet Therapy**

| | Mechanism of Action | Typical Dose/Route of Administration | Onset/Peak/ Duration | Specific Side Effects | Remarks |
|---|---|---|---|---|---|
| **Aspirin® (ASA)** | Irreversibly acetylates COX, inhibiting TXA2 synthesis, thus inhibiting platelet aggregation | Single loading 200-300 mg PO, followed by dose of 75-100 mg PO daily | Onset: 5-30 min<br>Peak: 0.25-3 h<br>Duration: 3-6 h (platelet inhibition lasts 7-10 d) | GI ulcer/bleeding<br>Tinnitus<br>Bronchospam<br>Angioedema<br>Reye's syndrome in pediatric patients | Indicated for stroke/MI prophylaxis<br>Reduce incidence of recurrent MI<br>Decrease mortality in post-MI patients<br>Contraindicated in patients with GI ulcers |
| **Aggrenox® (ASA + Dipyridamole)** | Dipyridamole increases intracellular cAMP levels, which inhibits TXA2 synthesis, leading to decreased platelet aggregation | 1 capsule PO bid | Peak: 75 min | H/A<br>Dyspepsia<br>N/V<br>Abdominal pain<br>Cardiac failure<br>Hemorrhoids | More effective than ASA in secondary prevention of stroke<br>Dipyridamole potentiates antiplatelet action of ASA |
| **Clopidogrel (Plavix®)** | Irreversibility inhibit ADP binding to platelets, thus decreased platelet aggregation | Loading dose 300 mg PO, then 75 mg daily | Onset: 2 h (loading dose)<br>Peak: 6 h (loading dose)<br>Duration: 5 d | URI<br>Chest pain<br>H/A<br>Flu-like syndrome<br>Depression<br>UTI<br>GI hemorrhage<br>Pancytopenia<br>May cause TTP | Prevention of cardiovascular events in high-risk patients<br>Clopidogrel is a prodrug requiring two-step activation to active metabolite<br>CYP2C19 poor metabolizers have diminished response to clopidrogrel<br>Caution with hepatic/renal impairment |
| **Prasugrel (Effient®)** | Same as clopidogrel | Loading dose 60 mg, then 5-10 mg PO daily | Onset: 30 min (loading dose)<br>Peak: 4 h (loading dose)<br>Duration: 5-10 d | Dizziness<br>H/A<br>Nervousness<br>Blurry vision | Alternative to clopidogrel for prevention of cardiovascular events in high-risk patients<br>Higher potency compared to clopidogrel<br>No significant drug-drug interaction, although more data is required |

**Table 40. Antiplatelet Therapy** (continued)

| | Mechanism of Action | Typical Dose/Route of Administration | Onset/Peak/ Duration | Specific Side Effects | Remarks |
|---|---|---|---|---|---|
| **Ticagrelor (Brilinta®)** | Reversibly inhibit ADP binding to platelets | Loading dose 180 mg, then 90 mg PO bid | Onset: 30 min (loading dose) Peak: 1.5 h for prodrug, 2.5 h for active metabolite | Difficulty or laboured breathing Shortness of breath Tightness in chest Dizziness | Alternative to clopidogrel for prevention of cardiovascular events in high-risk patients Higher potency compared to clopidogrel Ticagrelor is a prodrug that requires CYP3A4-mediated activation to active metabolite Drug-drug interactions with CYP3A4 inhibitors and inducers |
| **Glycoprotein IIb/IIIa Inhibitors (Reopro® [abciximab], Integrelin® [epti])** | Blocking GP II/IIIa receptor inhibits fibrinogen and vWF binding, leading to decreased platelet aggregation | Variable IV | Variable | Hypotension Back pain N/V Chest pain Abdominal pain Thrombocytopenia | Used most commonly in cardiac catheterization Contraindicated in PUD Monitoring aPTT/activated clotting time |

# Anticoagulant Therapy

**Table 41. Anticoagulant Therapy**

| | Mechanism of Action | Dose/Route of Administration | Onset/Peak/Duration | Reversing Agent | Monitoring | Specific Side Effects | Remarks |
|---|---|---|---|---|---|---|---|
| **Heparin** | Inhibition of FXa and FIIa, mediated via antithrombin | Variable, depends on indication; can be used IV or SC | Onset: Immediate (IV); 20-30 min (SC) | Protamine sulfate | aPTT (intrinsic pathway), UFH (anti-Xa) levels | Hemorrhage HIT Increased liver enzymes | Pregnancy: safe (does not cross placenta) |
| **Warfarin** | Vitamin K antagonist: inhibits production of II, VII, IX, X, proteins C and S | Individualized dosing by monitoring PT/INR; PO | Onset: 24-72 h Peak: 5-7 d Duration: 2-5 d | Vitamin K PCC FP | INR: maintain 2-3 (2.5-3.5 for certain mechanical valves) | Hemorrhage Cholesterol embolism syndrome Intraocular hemorrhage | Pregnancy: not used, can cross placenta (teratogenic) |
| **LMWH (enoxaparin, dalteparin, tinzaparin)** | Mainly FXa inhibition, some FIIa inhibition, both mediated via antithrombin | Variable, weight-based dose, depends on indication; SC/IV | Onset: 1-2 h Peak: 3-5 h Duration: 12-24 h | Partial reversibility with protamine sulfate | Anti-Xa levels in pediatrics, pregnancy and weight >150 kg | Hemorrhage Fever Increased liver enzymes <1% HIT | Increased bioavailability than heparin Can accumulate in patients low CrCl (<30 mL/min) Standard treatment of VTE in patients with malignancy |
| **Fondaparinux** | Selective FXa inhibition, mediated via antithrombin | Variable SC daily | Onset: 2 h Peak: 2-3 h | Not reversible | None | Anemia Fever Nausea Rash | Long half-life (17-21 h) Contraindicated in renal failure |
| **Rivaroxaban** | Direct FXa inhibitor | Variable, depends on indication; PO | Peak: 2-4 h | Andexanet alpha | Anti-Xa levels validated for Rivaroxaban may be used to detect presence of drug only | Syncope GI hemorrhage Menorrhagia | Indicated for treatment of acute VTE, secondary VTE prevention, thromboprophylaxis in orthopedic patients and stroke prophylaxis in non-valvular AFib; ensure CrCl>30 mL/min; must be taken with food; contraindicated in mechanical heart valves |
| **Apixaban** | Direct FXa inhibitor | PO bid | Onset: 3-4h Peak: 3-4 h | Andexanet alpha | Anti-Xa levels validated for Apixaban may be used to detect presence of drug only | Hemorrhage Nausea Anemia | Indicated for treatment of acute VTE, secondary VTE prevention, thromboprophylaxis in orthopedic patients and stroke prophylaxis in non-valvular AFib; ensure CrCl >25 ml/min; contraindicated in mechanical heart valves |
| **Argatroban** | Direct thrombin inhibitor | Variable IV | Onset: 5-10 min Duration: 20-40 min | Not reversible | aPTT | Dyspnea Hypotension Fever | Indicated for treatment of heparin-induced thrombocytopenia, PCI; contraindicated in mechanical heart valves |
| **Dabigatran** | Direct thrombin inhibitor | 150 mg PO bid | Peak: 1 h | Not reversible | Dilute thrombin time may be used to detect presence of drug only; TT also sensitive for drug presence | GI upset Dyspepsia | Indicated for treatment of acute VTE (after 5-10 d parenteral therapy), secondary VTE prevention, thromboprophylaxis in orthopedic patients and stroke prophylaxis in non-valvular AFib; ensure CrCl>30 mL/min; should be stored in blister pack; contraindicated in mechanical heart valves |

### Adverse Reactions of Heparin

- hemorrhage: depends on dose, age, and concomitant use of antiplatelet agents or thrombolytics
- heparin-induced thrombocytopenia a hematologic emergency associated with venous or arterial thrombosis (see Table 22, H29)
- osteoporosis: with long-term use

### Low Molecular Weight Heparin (enoxaparin, dalteparin, tinzaparin)

- increased bioavailability compared to unfractionated heparin
- increased duration of action
- SC route of administration
- do not need to monitor aPTT
- adverse reactions less common than UFH
- patients with renal failure (CrCl <30 mL/min) can accumulate LMWH, therefore must adjust dose
- only partially reversible with protamine sulfate
- HIT is less common

**Table 42. Recommended Therapeutic INR Ranges for Common Indications for Vitamin K Antagonists (Warfarin)**

| Indication | INR Range |
|---|---|
| Prophylaxis of venous thrombosis (high-risk surgery) | 2.0-3.0 |
| Treatment of venous thrombosis | |
| Most cases of thrombosis with antiphospholipid antibody syndrome | |
| Treatment of pulmonary embolism | |
| Prevention of systemic embolism | |
| Tissue heart valves | |
| AMI (to prevent systemic embolism) | |
| Valvular heart disease | |
| Atrial fibrillation | |
| Bileaflet mechanical valve in aortic position | |
| Mechanical prosthetic mitral valves (high risk) | 2.5-3.5 |

AMI = acute myocardial infarction

**Table 43. Recommended Management of a Supratherapeutic INR**

| INR | Bleeding Present | Recommended Action |
|---|---|---|
| **>Therapeutic to 4.5** | No | Lower warfarin dose OR Omit a dose and resume warfarin at a lower dose when INR is in therapeutic range OR No dose reduction needed if INR is minimally prolonged |
| **>4.5 to 10.0** | No | Omit the next 1 to 2 doses of warfarin, monitor INR more frequently and resume treatment at a lower dose when INR is in therapeutic range OR Omit a dose and administer 1 to 2.5 mg oral vitamin K in patients with increased risk of bleeding |
| **>10.0** | No | Hold warfarin and administer 5 to 10 mg oral vitamin K; monitor INR more frequently and administer more vitamin K as needed; resume warfarin at a lower dose when INR is in therapeutic range |
| **Any** | Serious or life threatening | Hold warfarin and administer 10 mg vitamin K by slow IV infusion; supplement with four-factor prothrombin complex concentrate; monitor and repeat as needed |

Adapted from: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;(2 suppl):e152S

# Chemotherapeutic and Biologic Agents Used in Oncology

**Table 44. Selected Chemotherapeutic and Biologic Agents**

| Class | Example | Mechanism of Action or Target |
|---|---|---|
| **Alkylating Agent** | • chlorambucil, cyclophosphamide, melphalan (nitrogen mustards)<br>• carboplatin, cisplatin<br>• dacarbazine, procarbazine<br>• busulfan<br>• bendamustine | Damage DNA via alkylation of base pairs<br>Leads to cross-linking of bases, abnormal base-pairing, DNA breakage |
| **Antimetabolites** | • methotrexate (folic acid antagonist)<br>• 6-mercaptopurine, fludarabine (purine antagonist)<br>• 5-fluorouracil (5-FU) (pyrimidine antagonist)<br>• hydroxyurea<br>• cytarabine | Inhibit DNA synthesis |
| **Antibiotics** | • adriamycin (anthracycline)<br>• bleomycin<br>• mitomycin C<br>• daunorubicin | Interfere with DNA and RNA synthesis |
| **Taxanes** | • paclitaxel<br>• docetaxel | Stabilize microtubules against breakdown once cell division complete |
| **Vinca-alkaloids** | • vinblastine<br>• vincristine<br>• vinorelbine | Inhibit microtubule assembly (mitotic spindles), blocking cell division |
| **Topoisomerase Inhibitors** | • irinotecan, topotecan (topo I)<br>• etoposide (topo II) | Interfere with DNA unwinding necessary for normal replication and transcription |
| **Steroids** | • prednisone<br>• dexamethasone | Immunosuppression |
| **Purine Analogues** | • fludarabine<br>• cladribine | Interferes with DNA synthesis |
| **Monoclonal Antibodies** | • trastuzumab (Herceptin®)<br>• bevacizumab (Avastin®)<br>• rituximab (Rituxan®), ofatumumab (Arzerra®), obinutuzumab (Gayzva®)<br>• cetuximab (Erbitux®)<br>• Daratumumab | HER2 antagonist<br>VEGF antagonist<br>CD20 antagonist<br>EGFR antagonist<br><br>CD38 antagonist |
| **Small Molecule Inhibitors** | • imatinib mesylate (Gleevec®)<br>• dasatinib<br>• nilotinib<br>• Bosutinib<br>• erlotinib (Tarceva®)<br>• gefitinib (Iressa®)<br>• bortezomib (Velcade®)<br>• sunitinib (Sutent®)<br>• ibrutinib (Imbruvica®)<br>• idealasib (Zyedlig®)<br>• ruxolitinib (Jakavi®)<br>• ponatinib (Iclusig®)<br>• Venetoclax<br>• Lenalidomide, Pomalidomide | *Bcr-Abl* inhibitor<br>*Bcr-Abl* inhibitor<br>*Bcr-Abl* inhibitor<br>*Bcr-Abl* inhibitorEGFR antagonist<br>EGFR antagonist<br>EGFR antagonist<br>26S proteasome inhibitor<br>VEGFR, PDGFR antagonist<br>BTK inhibitor<br>P13K inhibitor<br>JAK2 inhibitor<br>*Bcr-Abl* inhibitor<br>Immunomodulator |
| **CAR T cell therapy** | • tisagenlecleucel (Kymriah®)<br>• axicabtagene ciloleucel (Yescarta®) | Target CD19 |

# Landmark Hematology Trials

| Trial | Reference | Results |
|---|---|---|
| **Hematologic Malignancies and Related Disorders** | | |
| Hodgkin Lymphoma: ABVD vs. MOPP | *NEJM* 1992;327:1478-84 | In Hodgkin lymphoma, ABVD regimen has equal failure-free and overall survival to MOPP + ABVD, but less myelotoxicity; ABVD is standard chemotherapy for Hodgkin lymphoma |
| CHOP | *NEJM* 1993;328:1002-6 | In NHL, CHOP has lowest incidence of fatal toxic reactions and shows no significant difference from 3 other regimens in response or disease-free/overall survival; CHOP is the standard for advanced NHL |
| R-CHOP | *NEJM* 2002;346:235-42 | Addition of rituximab to CHOP increases complete response rate and prolongs event-free survival and overall survival in elderly with DLBCL |
| CML: Imatinib vs. IFN + Cytarabine | *NEJM* 2003;348:994-1004 | In patients with chronic-phase CML, imatinib was more effective than IFNα + cytarabine in inducing cytogenetic response and freedom from progression to accelerated phase/blast crisis |
| AZA-001 | *Lancet Oncol* 2009;10:223-32 | Azacitidine increases overall survival in higher-risk myelodysplastic syndrome than conventional care |
| CLL8 | *Lancet* 2010;376:1164-74 | Rituximab plus fludarabine and cyclophosphamide (FCR) improves progression-free and overall survival compared with fludarabine and cyclophosphamide alone (FC) in the treatment of CLL |
| VISTA | *JCO* 2010;28:2259-66 | Bortezomib plus melphalan and prednisone (MPV) is superior to melphalan and prednisone (MP) in overall survival of non-transplant-eligible multiple myeloma patients |
| MInT Group | *Lancet* 2011;12:1013-22 | Rituximab added to CHOP-like chemotherapy improved long-term outcomes for young patients with good-prognosis DLBCL |
| StIL | *Lancet* 2013;381(9873):1203-10 | Bendamustine plus rituximab is superior to R-CHOP in terms of progression-free survival and fewer toxic effects in patients with previously untreated indolent lymphoma |
| Ibrutinib vs. Ofatumumab in previously treated CLL | *NEJM* 2014;371:213-23 | Ibrutinib, as compared with ofatumumab, significantly improved progression-free survival, overall survival, and response rate among patients with previously treated CLL or SLL |
| ENDEAVOR | *Lancet Oncol* 2017;18(10):27 | Carfilzomib, as compared with bortezomib, significantly improved progression-free and overall survival in patients with relapsed or refractory multiple myeloma |
| Obinutuzumab for the First-Line Treatment of Follicular Lymphoma (GALLIUM) | *NEJM* 2017;377(14):1331 | Obinutuzumab (anti-CD20 monoclonal antibody), as compared with rituximab, improved progression-free survival for patients with advanced-stage follicular lymphoma |
| Phase I trial of Chimeric Antigen Receptor T cell (CAR-T) therapy for relapsed or refractory B-cell ALL | *NEJM* 2018;378(5):449-59 | CAR-T therapy achieved complete remission in 83% of patients in remission or refractory to previous treatment. Median survival was 12.9 mo. Typical median survival is 6 mo |
| **Thrombosis** | | |
| CLOT | *NEJM* 2003;349:146-53 | In patients with cancer and acute venous thromboembolism, LWMH was more effective than warfarin in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding |
| PT1 | *NEJM* 2005;353:85-86 | Hydroxyurea plus low-dose ASA is superior to anagrelide plus low-dose ASA for patients with essential thrombocythemia at high risk for vascular events |
| ESPIRIT | *Lancet* 2006;367:1665-73 | ASA plus dipyridamole is recommended over ASA alone as antithrombotic therapy after cerebral ischemia of arterial origin |
| Dabigatran vs. Warfarin in VTE | *NEJM* 2009;361:2342-52 | In the treatment of venous thromboembolism, dabigatran is as effective as warfarin and also has a similar safety profile; note: many problems in the trial, making it less pivotal in having drug approval |
| EINSTEIN-PE | *NEJM* 2012;366:1287-97 | Among patients with acute PE, rivaroxaban is noninferior to warfarin in preventing recurrent VTE, and is associated with similar bleeding rates |
| AMPLIFY | *NEJM* 2013;369:799-808 | In patients with VTE who have completed 6-12 mo of anticoagulation, long-term apixaban treatment reduces recurrent VTE or all-cause mortality without increasing rates of major bleeding |
| RE-VERSE AD | *NEJM* 2015;373:511-20 | Idarucizumab for dabigatran reversal |
| **Blood Products and Transfusion** | | |
| Platelet Transfusion Threshold | *NEJM* 1997;337:1870-75 | The risk of major bleeding in patients with AML undergoing induction chemotherapy was similar whether the platelet-transfusion threshold was set at 20 or 10; use of the lower threshold reduced platelet usage by 21.5% |
| TRICC BP | *NEJM* 1999;340:409-17 | A restrictive strategy of red-cell transfusion (when Hb <70) is at least as effective as and possibly superior to a liberal transfusion strategy (when Hb <100) in ICU patients; one possible exception is patients with an acute MI or unstable angina |
| Dose of Platelet Transfusion | *NEJM* 2010;362:600-13 | Low dose prophylactic platelet transfusion decreases total number of platelets transfused but increases number of transfusions but not incidence of bleeding in patients with hypoproliferative thrombocytopenia |
| Transfusion in High-Risk Patients after Hip Surgery | *NEJM* 2011;365:2453-62 | A liberal transfusion strategy (Hb <100), as compared with a restrictive strategy (anemia symptoms or at physician discretion for Hb<80), did not reduce rates of death or inability to walk independently on 60 d follow-up or reduce in-hospital morbidity in elderly patients at high cardiovascular risk |
| Therapeutic Platelet Transfusion | *Lancet* 2012;380:1309-16 | Therapeutic platelet transfusions (when bleeding occurs) may be used if severe bleeding can be identified early in autologous stem-cell transplant patients; prophylactic transfusion (when platelets <10) should remain standard of care in AML patients |
| Transfusion Strategies for Acute Upper GI Bleeding | *NEJM* 2013;368:11-21 | As compared with a liberal transfusion strategy (Hb <90), a restrictive strategy (Hb<70) significantly improved outcomes in patients with acute upper gastrointestinal bleeding |
| **Other** | | |
| MSH | *NEJM* 1995;332:1317-22 | Hydroxyurea is effective in reduction of complications and clinical manifestations of sickle cell disease |
| ITP: Dexamethasone | *NEJM* 2003;349:831-36 | A 4 d course of high-dose dexamethasone is effective initial therapy for adults with immune thrombocytopenic purpura |
| CRASH-2 | *Health Technol Assess* 2013; 17(10):1-79 | Early administration of TXA safely reduced the risk of death in bleeding trauma patients and is highly cost-effective. Treatment beyond 3 hours of injury is unlikely to be effective |

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# ID Infectious Diseases

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# Acronyms

| | |
|---|---|
| Abx | antibiotics |
| AFB | acid-fast bacilli |
| AIDS | acquired immune deficiency syndrome |
| ANC | absolute neutrophil count |
| AOM | acute otitis media |
| ARV | anti-retroviral |
| ART | anti-retroviral therapy |
| BAL | bronchoalveolar lavage |
| BCG | Bacille Calmette-Guérin |
| C&S | culture and sensitivity |
| CFU | colony forming units |
| CLIA | ChemiLuminescent ImmunoAssay |
| CLL | chronic lymphocytic leukemia |
| CMIA | ChemiLuminescent Microparticle ImmunoAssay |
| CMV | cytomegalovirus |
| CNS | central nervous system |
| CSF | cerebrospinal fluid |
| DEET | N,N-Diethyl-meta-toluamide |
| DM | diabetes mellitus |
| DVT | deep vein thrombosis |
| EBV | Epstein-Barr virus |
| EHEC | enterohemorrhagic *E. coli* |
| EIA | enzyme immunoassay |
| EIEC | enteroinvasive *E. coli* |
| ETEC | enterotoxigenic *E. coli* |
| FDP | fibrinogen degradation products |
| FTA-ABS | fluorescent Treponema antibody-absorption |
| FUO | fever of unknown origin |
| GAS | group A *Streptococcus* |
| GBS | group B *Streptococcus* |
| GC | gonococcus |
| GNB | Gram-negative bacilli |
| GP | Gram-positive |
| H. flu | *Haemophilus influenzae* |
| HAART | highly active anti-retroviral treatment |
| HAV | hepatitis A virus |
| HBc | HBV core antigen |
| HBeAg | HBV envelope antigen |
| HBsAg | HBV surface antigen |
| HBV | hepatitis B virus |
| HCC | hepatocellular carcinoma |
| HCV | hepatitis C virus |
| HDV | hepatitis D virus |
| HEV | hepatitis E virus |
| HHV | human herpes virus |
| Hib | *Haemophilus influenzae* b |
| HIV | human immunodeficiency virus |
| HPF | high power field |
| HRIg | human rabies immunoglobulin |
| HSV | herpes simplex virus |
| HUS | hemolytic uremic syndrome |
| IE | infective endocarditis |
| IFN | interferon |
| Ig | immunoglobulin |
| INH | isoniazid |
| IVDU | intravenous drug use |
| KOH | potassium hydroxide |
| KSHV | Kaposi's sarcoma-associated herpes virus |
| LOC | level of consciousness |
| LP | lumbar puncture |
| MERS | Middle Eastern respiratory syndrome |
| MDR | multidrug resistance |
| MHA-TP | microhemagglutination assay *T. pallidum* |
| MMR | measles/mumps/rubella |
| MRSA | methicillin-resistant *S. aureus* |
| MSM | men who have sex with men |
| MSSA | methicillin-sensitive *S. aureus* |
| O&P | ova and parasites |
| PCR | polymerase chain reaction |
| PMN | polymorphonuclear leukocytes |
| PNS | peripheral nervous system |
| PPD | purified protein derivative |
| RPR | rapid plasma reagin |
| RSV | respiratory syncytial virus |
| RTI | respiratory tract infection |
| RT-PCR | reverse transcription-PCR |
| SARS | severe acute respiratory syndrome |
| sBP | systolic blood pressure |
| SCID | severe combined immunodeficiency |
| SIADH | syndrome of inappropriate antidiuretic hormone secretion |
| Sn | sensitivity |
| Sp | specificity |
| spp. | species |
| SRI | severe respiratory illness |
| STEC | Shiga toxin-producing *E. coli* |
| STI | sexually transmitted infection |
| TB | *Mycoplasma tuberculosis* |
| Tlg | tetanus immune globulin |
| TMP/SMX | trimethoprim-sulfamethoxazole |
| TNF | tumour necrosis factor |
| TORCH | toxoplasmosis, other, rubella, cytomegalovirus, HSV |
| TPI | *T. pallidum* immobilization test |
| TPPA | *T. pallidum* particle agglutination assay |
| TSS | toxic shock syndrome |
| URTI | upper respiratory tract infection |
| UTI | urinary tract infection |
| VDRL | venereal disease research laboratory |
| VRE | vancomycin-resistant *Enterococcus* |
| VZV | varicella-zoster virus |

# Principles of Microbiology

## Bacteriology

### Bacteria Basics

- bacteria are prokaryotic cells that divide asexually by binary fission
- Gram stain divides most bacteria into two groups based on their cell wall
  - Gram-positive (GP): thick, rigid layer of peptidoglycan
  - Gram-negative (GN): thin peptidoglycan layer + thicker outer membrane composed of lipoproteins and lipopolysaccharides
  - clinical significance: GN thick outer membrane makes it resistant to penicillin's mechanism of action
- acid-fast bacilli (AFB): high mycolic acid content in cell wall, "acid fast" as washout phase with acid-alcohol is ineffective in acid-fast bacteria (e.g. *Mycobacteria*, *Nocardia)*
- "atypical" bacteria: not seen on Gram stain and difficult to culture
  - obligate intracellular bacteria: e.g. *Chlamydia*, *Chlamydophilia*
  - bacteria lacking a cell wall: e.g. *Mycoplasma*
  - spirochetes: e.g. *Treponema pallidum*
- $O_2$ can be either vital or detrimental to growth
  - obligate aerobes: require $O_2$
  - obligate anaerobes: require environment without $O_2$
  - facultative anaerobes: can survive in environments with or without $O_2$

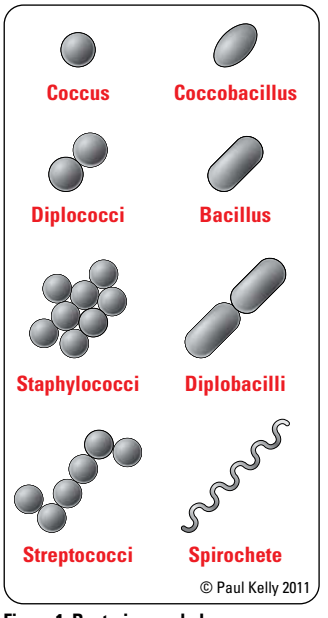



**Figure 1. Bacteria morphology**

### Mechanisms of Bacterial Disease

1. Adherence to and colonization of skin or mucous membranes
   - fimbriae (pili): microfilaments extending through the cell wall attach to epithelial cells (e.g. *E. coli* in the urinary tract)
2. Invasion or crossing epithelial barriers
3. Evasion of host defense system through inhibition of:
   - phagocytic uptake via polysaccharide capsule (e.g. *S. pneumoniae*, *N. meningitidis*, *H. influenzae*)
   - surface proteins (e.g. *Staphylococcus*, *Streptococcus*)
4. Toxin production
   - exotoxins are secreted by living pathogenic bacteria and cause disease even if the bacteria is not present (e.g. *Clostridium*)
   - endotoxins are structural components of GN bacterial cell walls, and may be shed by live cells or released during cell lysis
5. Intracellular growth
   - obligate intracellular: Rickettsia, *Chlamydia*, *Chlamydophilia*
   - facultative intracellular: *Salmonella*, *Neisseria*, *Brucella*, *Mycobacteria*, *Listeria*, *Legionella*
6. Biofilm
   - an extracellular polysaccharide network forming mesh around the bacteria (e.g. *S. epidermidis*) which can coat prosthetic devices such as IV catheters

## Table 1. Common Bacteria

| | Gram-Positive Bacteria | | Gram-Negative Bacteria | | Not Seen on Gram Stain | |
|---|---|---|---|---|---|---|
| | **Cocci** | **Bacilli (rods)** | **Diplococci** | **Bacilli (rods)** | **Acid Fast** | **Others** |
| **Aerobes** | *Staphylococcus*<br>*S. aureus*<br>*S. saprophyticus*<br>*S. epidermidis*<br>*S. lugdunensis*<br>*Streptococcus*<br>*S. pneumoniae*<br>*S. pyogenes* (GAS)<br>*S. agalactiae* (GBS)<br>*S. anginosis* group<br>*Enterococcus*<br>*E. faecalis* | *Bacillus*<br>*B. anthracis*<br>*Listeria*<br>*Nocardia* (modified acid-fast positive) | *Neisseria*<br>*N. meningiditis*<br>*N. gonorrhoeae*<br>*Moraxella*<br>*M. catarrhalis* | *Enterobacteriaceae*<br>*E. coli*<br>*Salmonella*<br>*Shigella*<br>*Campylobacter*<br>*Yersinia*<br>*Klebsiella*<br>*Legionella*<br>*Pseudomonas*<br>*Haemophilus*<br>*H. influenzae* | *Mycobacteria*<br>*M. tuberculosis*<br>*M. leprae*<br>*M. avium* complex | Obligative intracellular<br>*Rickettsiae*<br>*Chlamydia*<br>*C. trachomatis*<br>*Chlamydophila*<br>*C. pneumoniae*<br><br>No cell wall<br>*Mycoplasma*<br><br>Spirochaete (spiral)<br>*Treponema pallidum* |
| **Anaerobes** | *Peptostreptococcus*<br>*Cutibacterium (Propionibacterium)* acnes | *Clostridium*<br>*C. difficile*<br>*C. tetani*<br>*C. botulinum*<br>*C. perfringens* | | *Bacteroides*<br>*B. fragilis* | | |

## Table 2. Commensal Flora

| Site | Organisms |
|---|---|
| **Skin** | Coagulase-negative staphylococci, *Corynebacterium*, *C.* acnes, *Bacillus*, *S. aureus* |
| **Oropharynx** | Viridans group streptococci, *Haemophilus*, *Neisseria*, anaerobes (*Peptostreptococcus, Bacteroides, Veillonella, Fusobacterium, Actinomyces, Prevotella*) |
| **Small Bowel** | *E. coli*, anaerobes (low numbers) |
| **Colon** | *E. coli*, *Klebsiella*, *Enterobacter*, *Enterococcus*, anaerobes (*Bacteroides, Peptostreptococcus, Clostridium*) |
| **Vagina** | *Lactobacillus acidophilus*, viridans group streptococci, coagulase-negative staphylococci, facultative Gram-negative bacilli, anaerobes |

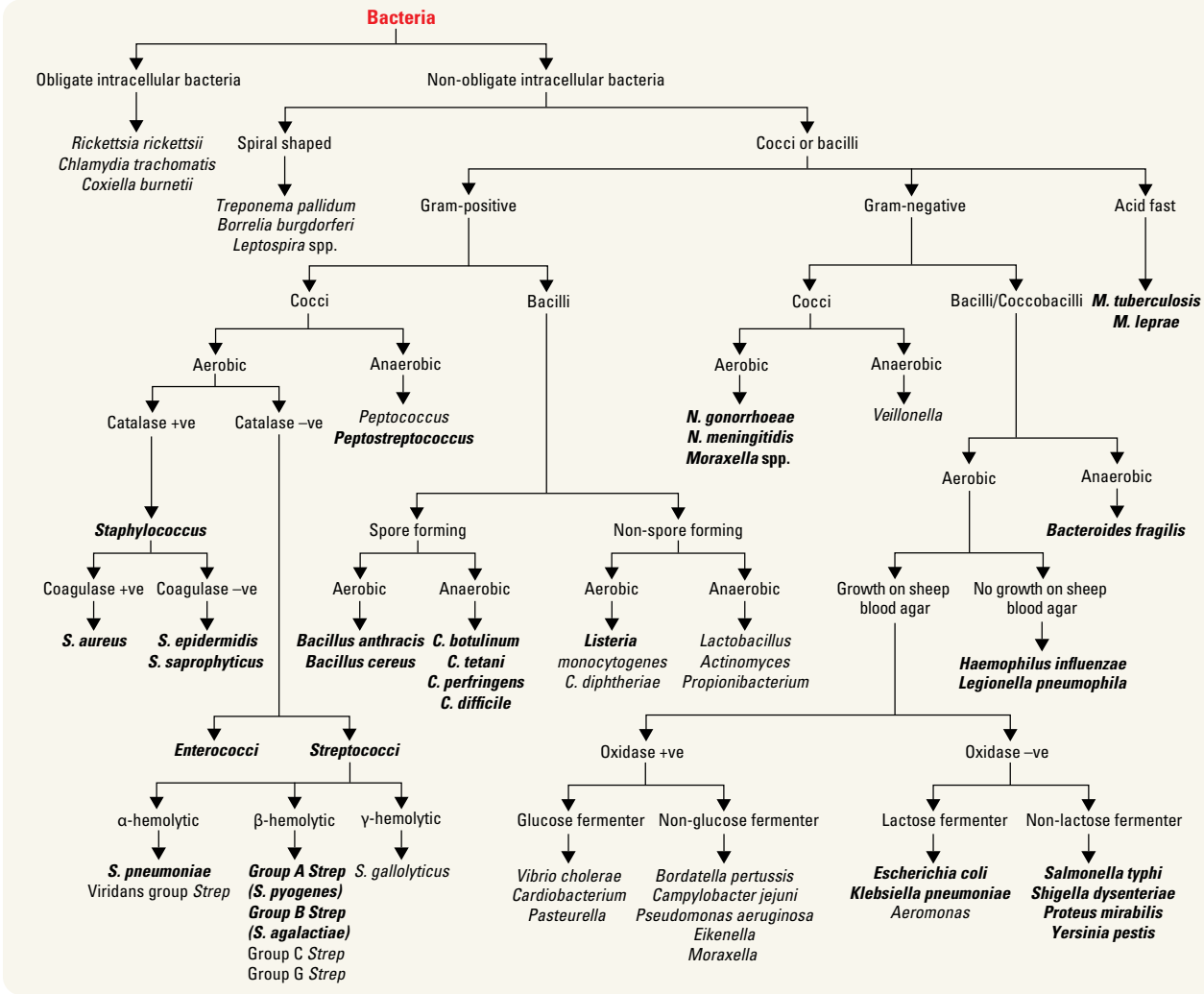



**Figure 2. Laboratory identification of bacterial species**

# Virology

## Viral Basics

- viruses are infectious particles consisting of RNA or DNA covered by a protein coat
  - infect cells and use host metabolic machinery to replicate
  - nucleic acid can be double stranded (ds) or single stranded (ss)
  - can be enveloped or naked
- virions are mature virus particles that can be released into the extracellular environment
- host susceptibility is governed by the host cell and virus surface proteins (viral tropism) and cellular immunity

## Viral Disease Patterns

1. acute infections (e.g. adenovirus)
   - host cells are lysed in the process of virion release
   - some produce acute infections with late sequelae (e.g. measles virus induced subacute sclerosing panencephalitis)
2. chronic infections (>6 mo): (e.g. HBV, HIV)
   - host cell machinery is used to produce and chronically release virions
3. latent infections
   - viral genome remains latent in host cell nucleus
   - can reactivate (e.g. HSV, VZV)

**Table 3. Common Viruses**

| Nucleic Acid | Enveloped | Virus Family | Major Viruses | Medical Importance |
|---|---|---|---|---|
| **dsDNA** | N | *Adenoviridae* | Adenovirus | URTI<br>Conjunctivitis<br>Gastroenteritis |
| | N | *Papillomaviridae* | HPV1,4<br>HPV6,11<br>HPV16,18, etc. | Plantar warts<br>Genital warts<br>Cervical/anal dysplasia and cancer |
| | Y | *Herpesviridae* | HHV1=HSV1<br>HHV2=HSV2<br>HHV3=VZV<br>HHV4=EBV<br>HHV5=CMV<br>HHV6*<br>HHV8=KSHV | Oral, ocular, and genital herpes; encephalitis<br>Genital, oral, and ocular herpes; encephalitis<br>Chicken pox, shingles<br>Mononucleosis, viral hepatitis<br>Retinitis, pneumonitis, hepatitis, encephalitis<br>Roseola<br>Kaposi's sarcoma, multicentric Castleman's disease, body cavity lymphoma |
| | N | *Polyomaviridae* | JC virus | Progressive multifocal leukoencephalopathy |
| | Y | *Hepadnaviridae*<br>*Poxviridae* | Hepatitis B<br>Variola | Hepatitis<br>Smallpox |
| **ssDNA** | N | *Parvoviridae* | Parvovirus B19 | Erythema infectiosum (Fifth disease) |
| **(+) ssRNA** | N | *Caliciviridae* | Norwalk<br>Hepatitis E | Gastroenteritis<br>Acute hepatitis |
| | N | *Picornaviridae* | Poliovirus<br>Echovirus<br>Rhinovirus<br>Coxsackie virus<br>Hepatitis A | Poliomyelitis<br>URTIs, viral meningitis<br>URTIs<br>Hand-foot-and-mouth, viral meningitis, myocarditis<br>Acute hepatitis |
| | Y | *Coronaviridae* | Coronavirus | URTIs, SARS, MERS |
| | Y | *Flaviviridae* | Yellow fever<br>Dengue fever<br>Hepatitis C<br>West Nile<br>Zika | Yellow fever<br>Dengue fever<br>Hepatitis<br>Encephalitis, flaccid paralysis<br>Zika virus disease |
| | Y | *Togaviridae* | Rubella<br>Chikungunya | Rubella (German measles)<br>Chikungunya |
| **(+) ssRNA-RT** | Y | *Retroviridae* | HIV<br>HTLV-1 | AIDS<br>T-cell leukemia and lymphoma |
| **(+) ssRNA** | Y | *Arenaviridae* | Lassa | Lassa fever |
| | Y | *Filoviridae* | Ebola, Marburg | Hemorrhagic fever |
| | Y | *Orthomyxoviridae* | Influenza A, B, C | Influenza |
| | Y | *Paramyxoviridae* | Measles<br>Mumps<br>Parainfluenza<br>RSV | Measles<br>Mumps<br>URTIs, croup, bronchiolitis<br>Bronchiolitis, pneumonia |
| | Y | *Rhabdoviridae* | Rabies | Rabies |
| **dsRNA** | N | *Reoviridae* | Rotavirus | Gastroenteritis |

Note: ___viridae = family, ___virus = genus, # = species (e.g. Retroviridae HIV-2)
*Roseolovirus, Herpes lymphotropic virus

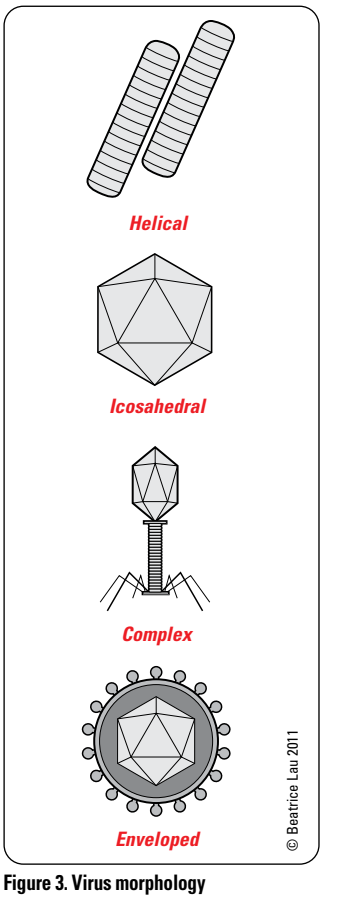



**Figure 3. Virus morphology**

**DNA Viruses: Families**

**HHAPPPPy**
***H**epadnaviradae*
***H**erpesviridae*
***A**denoviridae*
***P**apillomaviridae*
***P**arvoviridae*
***P**olyomaviridae*
***P**oxviridae*

# Mycology

## Fungal Basics

- fungi are eukaryotic organisms, they can have the following morphologies
  1. yeast (unicellular)
  2. moulds, i.e. filamentous fungi (multicellular with hyphae)
  3. dimorphic fungi (found as mould at room temperature but grow as yeast-like forms at body temperature)

**Table 4. Membrane and Cell Wall Compositions**

| | Membrane Sterol | Cell Wall |
|---|---|---|
| **Bacteria** | – | Peptidoglycan |
| **Human Cell** | Cholesterol | – |
| **Fungi** | Ergosterol | Chitin (complex glycopolysaccharide) |

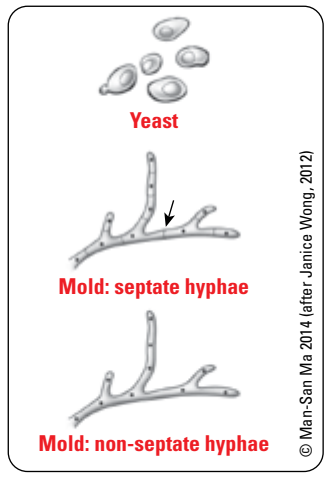



**Figure 4. Common fungus morphology**

## Mechanisms of Fungal Disease

- primary fungal infection by:
  - overgrowth of normal flora (e.g. *Candida* species)
  - inhalation of fungal spores
  - traumatic inoculation into skin
- toxins produced by fungi (e.g. ingestion aflatoxins)
- allergic reactions to fungi (e.g. bronchopulmonary aspergillosis)

# Parasitology

## Parasite Basics

- **parasite**: an organism that lives in or on another organism (host) and damages the host in the process
- parasites with complex life cycles require more than one host to reproduce
  - reservoir host: maintains a parasite and may be the source for human infection
  - intermediate host: maintains the asexual stage of a parasite or allows development of the parasite to proceed through the larval stages
  - definitive host: allows the parasite to develop to the adult stage where reproduction occurs
- 2 major groups of parasites: protozoa and helminths
- see Tables 24 and 25, ID37-38 for examples of clinically important parasites

**Table 5. Differences Between Protozoa and Helminths**

| Protozoa | Helminths |
|---|---|
| Unicellular | Multicellular |
| Motile trophozoite, inactive cyst | Adult → egg → larva |
| Multiplication | No multiplication in human host |
| Eosinophilia unusual | Eosinophilia (proportional to extent of tissue invasion)* |
| Indefinite life span | Definite life span |

*Adult Ascaris (roundworm) does not cause eosinophilia; migratory larval phases of Ascaris, however, cause high-grade eosinophilia

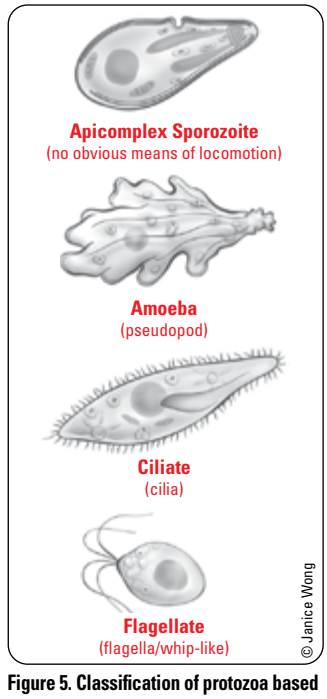



**Figure 5. Classification of protozoa based on movement**

## Characteristics of Parasitic Disease

- symptoms are usually proportional to parasite burden
- tissue damage is due to the parasite and host immune response
- chronic infections may occur with or without overt disease
- immunocompromised hosts are more susceptible to manifestations of infection, reactivation of latent infections, and more severe disease
- eosinophilia may suggest a parasitic infection

## Mechanisms of Parasitic Disease

1. Mechanical obstruction (e.g. ascariasis, clonorchiasis)
2. Competition with host for resources (e.g. anemia in hookworm disease, vitamin B12 deficiency in diphyllobothriasis)
3. Cytotoxicity leading to abscesses and ulcers (e.g. amoebiasis, leishmaniasis)
4. Inflammatory
   - acute hypersensitivity (e.g. pneumonitis in Loeffler's syndrome)
   - delayed hypersensitivity (e.g. egg granulomas in schistosomiasis)
   - cytokine-mediated (e.g. systemic illness of malaria, disseminated strongyloidiasis)
5. Immune-mediated injury
   - autoimmune (e.g. myocarditis of Chagas disease, tissue destruction of mucocutaneous leishmaniasis)
   - immune complex (e.g. nephritis of malaria, schistosomiasis)

Parasite sampling may need to be repeated on a number of occasions before infection can be ruled out

# Transmission of Infectious Diseases

**Table 6. Mechanism of Transmission**

| Mechanism | Mode of Transmission | Examples | Preventative Measure |
|---|---|---|---|
| **Contact** | Direct physical contact, or indirect contact with a fomite | Skin-to-skin (MRSA)<br>Sexual (*N. gonorrhoeae*, *C. trachomatis*, HSV, HIV)<br>Blood-borne (HIV, HBV, HCV) | For patients in health care facilities:<br>Contact precautions<br>Barrier precautions<br>Safe needlestick/sharp practices |
| **Droplet/ Contact** | Respiratory droplets (>5 μm) can be projected short distances (≤2 m) and deposit on mucosal surfaces of the recipient (e.g. by coughing, sneezing, or talking); transmission can also occur by direct physical contact of respiratory fluids or indirect contact with a fomite contaminated with respiratory fluids | Influenza, mumps<br>*N. meningitidis*, *Bordetella pertussis* | For patients in health care facilities:<br>Contact/droplet precautions |
| **Airborne** | Airborne droplet nuclei (<5 μm) remain infectious over time and distance | *M. tuberculosis*, disseminated VZV, measles | For patients in health care facilities:<br>Airborne precautions |
| **Food/ Waterborne** | Ingestion of contaminated food or water | *V. cholerae*, *Salmonella*, HAV, HEV | Prophylactic vaccinations where available<br>Ensure clean food/water supply<br>For patients in health care facilities:<br>Contact precautions used for admitted patients with fecal incontinence when stool is unable to be contained in diapers |
| **Zoonotic** | Disease transmission from animals to humans either directly or via an insect vector | Animals (rabies, Q fever)<br>Arthropods (malaria, Lyme disease, West Nile virus) | Prophylactic medications, vaccinations<br>Protective clothing, insect repellent, mosquito nets, tick inspection |
| **Vertical** | Spread of disease from parent to offspring | Congenital syndromes (TORCH infections)<br>Perinatal (HIV, HBV, GBS) | Prenatal screening<br>Prophylactic treatment |

# Nosocomial Infections

- **definition**: infections acquired >48 h after admission to a healthcare facility OR within 30 d from discharge
- **risk factors**: prolonged hospital stay, antibiotic use, surgery, hemodialysis, intensive care, colonization with a resistant organism, immunodeficiency
  - patients with nosocomial infections have higher mortality, longer hospital stays, and higher healthcare costs
- hand hygiene is an essential precaution

**Table 7. Common Nosocomial Infectious Agents**

| Bacteria | Characteristics | Manifestation | Investigations | Management |
|---|---|---|---|---|
| **Methicillin-Resistant *S. aureus* (MRSA)** | Gram-positive cocci | Skin and soft tissue infection<br>Bacteremia<br>Pneumonia<br>Endocarditis<br>Osteomyelitis | Admission screening culture from nares and peri-anal region identifies colonization<br>Culture of infection site<br>CXR | Contact precautions<br>For infection: vancomycin or daptomycin or linezolid<br>To decolonize: 2% chlorhexidine wash OD (+ rifampin + (doxycycline or TMP/SMX) + mupirocin cream bid to nares) x 7 d |
| **Vancomycin-Resistant *Enterococcus* (VRE)** | Majority are *E. faecium*<br>Resistant if minimum inhibitory concentration of vancomycin is ≥32 μg/mL | Rarely causes disease in healthy people<br>UTI<br>Bacteremia<br>Endocarditis<br>Meningitis | Rectal or perirectal swab OR stool culture for colonization<br>Culture of infected site | Contact precautions*<br>Ampicillin if susceptible<br>Otherwise, linezolid, tigecycline, or daptomycin depending on site of infection<br>No effective decolonization methods identified |
| ***Clostridium difficile* (*C. difficile*)** | Releases exotoxins A and B<br>Hypervirulent strain (NAP1/ B1/027) has been responsible for increase in incidence and severity | Fever, nausea, abdominal pain<br>Watery diarrhea<br>Pseudomembranous colitis<br>Severe: toxic megacolon<br>Risk of bowel perforation<br>Associated with antibiotic use<br>Leukocytosis | Stool PCR for toxin A and B genes<br>Stool immunoassay for toxins A and B (less sensitive than PCR)<br>AXR (may see colonic dilatation)<br>Sigmoidoscopy for pseudomembranes; avoid if known colonic dilatation | Contact precautions<br>Stop culprit antibiotic therapy (primarily fluoroquinolones and clindamycin)<br>Supportive therapy (IV fluids)<br>Empiric treatment with either vancomycin or fidaxomicin<br>If access to empiric treatment is limited, then metronidazole may be used<br>For fulminant *C. difficile* infection (previously called severe), oral vancomycin is used. IV metronidazole added to regimen if ileus present |
| **Extended Spectrum β-lactam Producers (ESBL producing** E. coli, K. *pneumoniae*) | Resistant to most β-lactam antibiotics except carbapenams e.g. penicillins, aztreonam,** and cephalosporins | UTI<br>Pulmonary infection<br>Bacteremia<br>Liver abscess in susceptible patients<br>Meningitis | Blood, sputum, urine, or aspirated body fluid culture<br>Imaging at infection site (CXR, CT, U/S) | Carbapenems or non-β-lactam antibiotics can be used for empiric therapy |

*The use of contact precautions for VRE varies depending on institutional policies. **Not available in Canada

# Respiratory Infections

## Pneumonia

• see Pediatrics, P83

### Definition
• infection of the lung parenchyma

### Etiology and Risk Factors
• impaired lung defenses
  ▪ poor cough/gag reflex (e.g. illness, drug-induced)
  ▪ impaired mucociliary transport (e.g. smoking, cystic fibrosis)
  ▪ immunosuppression (e.g. steroids, chemotherapy, AIDS/HIV, DM, transplant, cancer)
• increased risk of aspiration
  ▪ impaired swallowing mechanism (e.g. impaired consciousness, neurologic illness causing dysphagia, mechanical obstruction)
• no organism identified in 75% of hospitalized cases, and >90% of ambulatory cases

When *Klebsiella* causes pneumonia; see red currant jelly sputum

**3 As of *Klebsiella***
**A**spiration pneumonia
**A**lcoholics and diabetics
**A**bscess in lungs

**Table 8. Common Organisms in Pneumonia**

| Community-Acquired | Nosocomial | Aspiration | Immunocompromised Patients | Alcoholic |
|---|---|---|---|---|
| Typical Bacteria<br>*Streptococcus pneumoniae*<br>*Moraxella* catarrhalis<br>*Haemophilus influenzae*<br>*Staphylococcus aureus*<br>GAS<br>Atypical Bacteria<br>*Mycoplasma pneumoniae*<br>*Chlamydophila pneumoniae*<br>*Legionella pneumophila*<br>Viral<br>Influenza virus<br>Adenovirus | Enteric GNB (e.g. *E. coli*)<br>*Pseudomonas aeruginosa*<br>*S. aureus* (including MRSA) | Oral anerobes (e.g. *Bacteroides*)<br>Enteric GNB (e.g. *E. coli*)<br>*S. aureus*<br>Gastric contents (chemical pneumonitis) | *Pneumocystis jiroveci*<br>Fungi (e.g. *Cryptococcus*)<br>*Nocardia*<br>CMV<br>HSV<br>TB | *Klebsiella*<br>Enteric GNB<br>*S. aureus*<br>Oral anaerobes (aspiration)<br>TB |

*See **Pediatrics**, P84, Table for *Common Causes and Treatment of Pneumonia at Different Ages*

Aspiration pneumonias more commonly manifest as infiltrates in the right middle or lower lobes due to the larger calibre and more vertical orientation of the right bronchus

### Clinical Feature
• cough (± sputum), fever, pleuritic chest pain, dyspnea, tachypnea, tachycardia
• elderly often present atypically; altered LOC is sometimes the only sign
• evidence of consolidation (dullness to percussion, bronchial breath sounds, crackles)
• features of parapneumonic effusion (decreased air entry, dullness to percussion)
• complications: ARDS, lung abscess, parapneumonic effusion/empyema, pleuritis ± hemorrhage

### Investigations
• pulse oximetry to assess severity of respiratory distress
• CBC and differential, electrolytes, urea, Cr, ABG (if respiratory distress), troponin/CK, LFTs, urinalysis
• sputum Gram stain/C&S, blood C&S, ± serology/viral detection, ± pleural fluid C&S (if effusion >5 cm or respiratory distress)
• CXR ±CT chest shows distribution (lobar consolidation or interstitial pattern), extent of infiltrate ± cavitation
• bronchoscopy ± washings for:
  ▪ (1) severely ill patients refractory to treatment and (2) immunocompromised patients

**Does This Patient Have Ventilator-Associated Pneumonia?**
JAMA 2007;297:1583-1593
**Study**: Systematic review of articles describing the precision and accuracy of clinical, radiographic, and laboratory data to diagnose bacterial ventilator-associated pneumonia, which is the most common and fatal nosocomial complication of intensive care.
**Results**: The presence of a new infiltrate on radiography with 2 or more of purulent sputum, fever, or increased white blood cell count increases the likelihood of ventilator-associated pneumonia (LR 2.8, 95% CI 0.97-7.9). Fewer than 50% neutrophils on the cell count of lower pulmonary secretions make ventilator-associated pneumonia unlikely (LR 0.05-0.10).
**Conclusions**: Routine bedside evaluation with radiographic information provides suggestive, but not definitive, evidence of ventilator-associated pneumonia. Clinicians need to consider additional tests to provide further evidence for ventilator-associated pneumonia.

### Treatment
• ABC, $O_2$, IV fluids, consider salbutamol (nebulized or MDI)
• determine prognosis and need for hospitalization and antibiotics

### Criteria for Hospitalization

**Table 9. CURB 65 Score – Pneumonia Clinical Prediction Tool**

| Component* | Measurement(s) | Points | Total Score | Mortality | Disposition |
|---|---|---|---|---|---|
| **Confusion** | Altered mental status | 1 | 0-1 | <5% | Can treat as outpatient |
| **Urea/BUN** | Urea >7 mmol/L or BUN >20 mg/dL | 1 | 2-3 | 5-15% | Consider hospitalization |
| **Respiratory Rate** | >30 breaths/min | 1 | 4-5 | 15-30% | Consider ICU |
| **Blood Pressure** | Systolic <90 or diastolic <60 mmHg | 1 | | | |
| **Age** | 65 or older | 1 | | | |

* A CRB-65 score may be applied in the community as its criteria depend on clinical assessment alone

**Table 10. IDSA/ATS Community Acquired Pneumonia Treatment Guidelines 2007**

| Setting | Circumstances | Treatment |
|---|---|---|
| **Outpatient** | Previously well<br>No antibiotic use in last 3 mo | β-lactam[1], Macrolide[2]<br>OR Doxycycline<br>OR Omadacycline (for adult use only; not intended in pediatric population) |
| | Comorbidities[3]<br>Antibiotic use in last 3 mo (use different class) | β-lactam[1] ± Macrolide[2]<br>OR Respiratory fluoroquinolone[4] |
| **Inpatient** | Ward | β-lactam[1] ± Macrolide[2]<br>OR Respiratory fluoroquinolone[4]<br>OR Omadacycline (for adult use only; not intended in pediatric population) |
| | ICU | β-lactam[1] + (Macrolide[2] OR Respiratory fluoroquinolone[4]) |

*Given different regional resistance patterns, therapy should be based on local epidemiology and site-specific recommendations
**Refers to empiric treatment to be started. Appropriate antibiotic therapy should be tailored if pathogen is identified
1. **β-lactam**: cefotaxime, ceftriaxone, ampicillin-sulbactam
2. **Macrolide**: use azithromycin or clarithromycin
3. **Comorbidities**: chronic heart, lung, liver, or renal disease, DM, alcoholism, malignancy, asplenia, immunocompromised
4. **Respiratory fluoroquinolone**: moxifloxacin, gemifloxacin, levofloxacin
**IDSA**: Infectious Diseases Society of America
**ATS**: American Thoracics Society

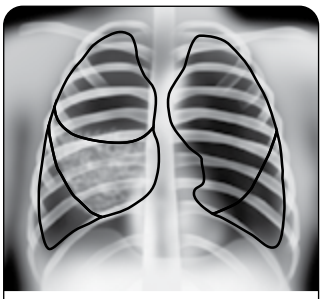
**Table 11. IDSA/ATS Hospital-Acquired (HAP) and Ventilator-Associated (VAP) Pneumonia Clinical Practice Guidelines 2016**

| Setting | Treatment |
|---|---|
| Clinically suspected **HAP** (non-VAP) with no increase in likelihood of MRSA and not at high risk of mortality | **One of**:<br>piperacillin-tazobactam<br>OR cefepime<br>OR levofloxacin<br>OR imipenem<br>OR meropenem |
| Clinically suspected **HAP** (non-VAP) with increasing likelihood of MRSA and not at high risk of mortality | **One of:**<br>piperacillin-tazobactam<br>OR cefepime or ceftazidime<br>OR levofloxacin or ciprofloxacin<br>OR imipenem or meropenem<br>OR aztreonam*****<br>**PLUS one of**:<br>vancomycin or linezolid for MRSA coverage |
| Clinically suspected **HAP** (non-VAP) with high risk of mortality or recipient of IV antibiotics in last 90 d | **Two of the following (avoid 2 β-lactams):**<br>piperacillin-tazobactam<br>OR cefepime or ceftazidime<br>OR levofloxacin or ciprofloxacin<br>OR imipenem or meropenem<br>OR aztreonam*****<br>OR amikacin or gentamicin or tobramycin<br>**PLUS either MRSA or MSSA coverage:**<br>MRSA: vancomycin or linezolid<br>OR MSSA: piperacillin-tazobactam, cefepime, levofloxacin, imipenem, meropenem |
| Clinically suspected **VAP** in units where empiric MRSA coverage and double antipseudomonal/ Gram-negative coverage are appropriate | **One of**:<br>β-lactam/β-lactamase inhibitor (piperacillin/tazobactam)<br>OR antipseudomonal cephalosporin (cefepime or ceftazidime)<br>OR antipseudomonal carbapenem (imipenem or meropenem)<br>OR monobactam (aztreonam*****)<br>**PLUS one of:**<br>antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin)<br>OR aminoglycoside (amikacin, gentamicin, or tobramycin)<br>OR polymyxins (colistin or polymyxin B)<br>**PLUS one of:**<br>vancomycin or linezolid for MRSA coverage |

**Refers to empiric treatment to be started. Appropriate antibiotic therapy should be tailored if pathogen is identified
*** Available in Canada through special access**
Risk factors for mortality include need for ventilatory support due to pneumonia and septic shock
Risk factors for MDR VAP: prior IV antibiotic use within 90 d, septic shock at time of VAP, ARDS preceding VAP, 5+ d of hospitalization prior to VAP onset, acute renal replacement therapy prior to VAP onset
Risk factors for MDR HAP, MRSA VAP/HAP or MDR *Pseudomonas* VAP/HAP: Prior IV antibiotic use within 90 d
**Note**: Indications for MRSA coverage includes IV antibiotic treatment during the prior 90 d and treatment in a unit where prevalence of MRSA of *S. aureus* isolates is not known or is >20%
**Note**: These guidelines may be less applicable in Canada given lower rates of antibiotic resistance among common nosocomial pathogens

## Prevention

- Public Health Agency of Canada recommends the following
  - vaccine for influenza A and B annually for all ages ≥6 mo
  - pneumococcal polysaccharide vaccine (Pneumovax®) for all adults >65 yr and in younger patients 24 mo of age and older at high risk for invasive pneumococcal disease (e.g. functional or anatomic asplenia, congenital or acquired immunodeficiency)
  - pneumococcal conjugate vaccine (Prevnar-13®) for all children <5 yr, and for children and adolescents at high risk for invasive pneumococcal disease who are 5-17 yr and who have not previously received Prevnar-13® (CDC recommends giving Prevnar-13® to all adults at high risk for invasive pneumococcal disease)



Lobar Pneumonia



Bronchopneumonia



Interstitial Pneumonia

©Stuart Jantzen 2012

**Figure 6. Lobar, broncho, and interstitial pneumonia**

**Does This Adult Patient Have Pneumonia? From The Rational Clinical Examination**
JAMA 2009; http://www.jamaevidence.com/content/3485708
**Study**: Systematic review of articles assessing the sensitivity and specificity of clinical exam maneuvers for the diagnosis of adult community acquired pneumonia.
**Results**: The presence of fever or immunosuppression had a positive likelihood ratio (+LR) of 2, while a history of dementia had a +LR of 3; however, these traits are not confirmatory. The presence of an abnormality in any vital sign, including tachycardia, tachypnea, or fever had a +LR ranging from 2-4, which was not significantly affected by different cut-points. The absence of vital sign abnormality had a –LR ranging from 0.5-0.8. The combination of respiratory rate <30/min, heart rate <100/min, and temperature <37.8°C had a –LR of 0.18. Findings on chest exam raised the likelihood of diagnosis, but were uncommonly seen in studies. For example, presence of asymmetric respirations essentially confirmed the diagnosis, but was only present in 4% of patients. In patients with a clinical diagnosis, but normal radiograph, only ~10% will develop radiographic findings in 72 h.
**Conclusions**: Evidence suggests no single item on clinical history or physical exam is sufficient to rule in or out pneumonia without chest x-ray. Vital sign abnormalities were correlated with a diagnosis of pneumonia. Findings on chest exam significantly raised the likelihood of pneumonia, but were uncommonly seen in studies.

# Influenza

## Definitions and Etiology

- influenza viruses A and B
- influenza A further divided into subtypes based on envelope glycoproteins
  - hemagglutinin (H) and neuraminidase (N)
- seasonal (epidemic) influenza
  - main circulating influenza viruses: influenza A (H1N1), influenza A (H3N2) and influenza B
  - associated with antigenic drift (gradual, minor changes due to random point mutations)
  - may create a new viral subtype resulting in a seasonal epidemic (disease prevalence is greater than expected)
  - outbreaks occur mainly during winter months (late December to early March)
- pandemic influenza
  - associated with antigenic shift: abrupt, major changes due to mixing of two different viral strains from different hosts
  - may create a new viral strain resulting in a pandemic outbreak (worldwide)
  - antigenic shift occurs only in type A
- transmission: droplet, possibly airborne

**Table 12. Difference Between Influenza Strains**

| | Influenza A | Influenza B |
|---|---|---|
| **Host(s)** | Humans, birds, mammals | Humans only |
| **Antigenic Drift** | Yes, new strains | Yes, new strains |
| **Antigenic Shift** | Yes, new subtypes | No |
| **Epidemics** | Yes | Yes |
| **Pandemics** | Yes | No |

## Clinical Feature

- incubation period 1-4 d and symptoms typically resolve in 7-10 d
- acute onset of systemic (fever, chills, myalgias, arthralgias, headache, fatigue) and respiratory symptoms (cough, dyspnea, pharyngitis)
- complications: respiratory (viral pneumonia, secondary bacterial pneumonia, otitis media, sinusitis), muscular (rhabdomyolysis, myositis), neurologic (encephalitis, meningitis, transverse myelitis, Guillain-Barré syndrome)
- severe disease more likely in the elderly, children, pregnant women, patients with immunocompromise, asthma, COPD, CVD, diabetes, and obesity

## Investigations

- diagnosis is primarily clinical based on symptoms during the influenza season
- nasopharyngeal swabs for RT-PCR (gold standard), or rapid antigen detection (DFA, direct fluorescent antigen) detection
- serology: rarely used for clinical management

## Treatment and Prevention

- primarily supportive unless severe infection or high-risk for complications
- neuraminidase inhibitors: oseltamivir (Tamiflu®) or zanamivir (Relenza®) for treatment and prophylaxis against types A and B
  - decreases duration (by ~1 d) and severity of symptoms if given within 48 h of onset
  - treatment beyond 48 h time window may be warranted in immunosuppressed and critically ill patients
- vaccine for influenza A and B viruses is recommended annually for all ages ≥6 mo
  - vaccine is reformulated each year to reflect circulating influenza A and B strains

## High Risk for Complications

- anyone who is hospitalized, patients with severe illness/chronic medical conditions, immunocompromised patients, children <2 yr, elders >65 yr, pregnant women or women ≥2 wk postpartum



**Beware! Do Not Confuse *H. influenzae* with Influenza Virus**

***H. influenzae***: a bacterium (Types A, B, C, D, E, F, refer to capsule)
**Influenza**: a virus (Types A and B refer to strain)



**Vaccines for Preventing Influenza in Healthy Adults**

Cochrane DB Syst Rev 2014;CD001269
**Study**: Meta-analysis of 90 RCTs and quasi-RCTs evaluating influenza vaccines compared to placebo in healthy individuals aged 16-65 yr.
**Results**: The preventative effect of inactivated influenza vaccine on healthy adults is small: 40 people would need a vaccination to avoid one influenza-like illness and 71 people would need a vaccination to prevent one case of influenza. 15.6% of unvaccinated versus 9.9% of vaccinated people developed influenza-like symptoms: of these participants, only 2.4% and 1.1%, respectively, developed laboratory-confirmed influenza. Vaccination had a modest effect on working days lost, but no effects on hospitalization or complications. The effectiveness of live aerosol vaccinations on healthy adults is similar to that of inactivated influenza vaccines: 46 people would need a vaccination to avoid one influenza-like illness.
**Conclusions**: Influenza vaccines have a very modest effect in reducing influenza-like illness and working days lost in the general population.



**Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection**

NEJM 2018;378:345-53.
**Objective**: To investigate the association between laboratory-confirmed influenza infection and acute MI.
**Methods**: Self-controlled case-series. Risk interval defined as first 7 d after respiratory specimen collection and control interval as 1 yr before and 1 yr after the risk interval.
**Results**: Increased incidence ratio of an admission for acute MI during risk interval vs. control interval (6.05, 95% CI 3.86-9.50). No increased incidence after 7 d. Increased incidence ratios for acute MI within 7 d after detection of influenza B (10.11, 95% CI 4.37-23.38), influenza A (5.17, 95% CI 3.02-8.84), and respiratory syncytial virus (3.51, 95% CI 1.11-11.12).
**Conclusions**: Significant association between respiratory infections, especially influenza, and acute MI.

# Skin and Soft Tissue Infections

## Cellulitis

### Definition
- acute infection of the skin principally involving the dermis and subcutaneous tissue

### Etiology
- common causative agents: β-hemolytic streptococci (by far the most common cause of non-purulent cellulitis) and occasionally *S. aureus* or *S. lugdunensis*
- immunocompromised patients or water exposure: may also include Gram-negative rods and fungi
- bite wounds: consider skin of "bitee" and mouth of "biter"
- risk factors
  - trauma with direct inoculation, recent surgery
  - peripheral vascular disease, lymphedema, DM, cracked skin in feet/toes (tinea pedis)

,
### Clinical Feature
- pain, edema, erythema with indistinct borders ± regional lymphadenopathy, systemic symptoms (fevers, chills, malaise)
- can lead to ascending lymphangitis (visible red streaking in skin along lymphatics proximal to area of cellulitis)

### Investigations
- CBC and differential, blood C&S if febrile
- skin swab ONLY if open wound with pus

### Treatment
- consult local guidelines for appropriate antibiotic therapy
- antibiotics: cephalexin (broader coverage if risk factors for Gram-negative rods)
- if extensive erythema or systemic symptoms, consider cefazolin IV
- if MRSA is suspected, empiric coverage for MRSA may be considered (see *A Simplified Look at Antibiotics*, ID44)
- limb rest and elevation may help reduce swelling

## Necrotizing Fasciitis

### Definition
- life- and limb-threatening infection of the deep fascia characterized by rapid spread

### Etiology
- two main forms
  - Type I: polymicrobial infection – aerobes and anaerobes (e.g. *S. aureus*, *Bacteroides*, *Enterobacteriaceae*)
  - Type II: monomicrobial infection with GAS, and less commonly *S. aureus*

### Clinical Feature
- pain out of proportion to clinical findings and beyond border of erythema
- edema, ± crepitus (subcutaneous gas from anaerobes), ± fever
- infection spreads rapidly
- patients may rapidly become very sick (tachycardia, hypotension, lightheadedness)
- late findings
  - skin turns dusky blue and black (secondary to thrombosis and necrosis)
  - induration, formation of hemorrhagic bullae

### Investigations
- clinical/surgical diagnosis – do NOT wait for results of investigations before beginning treatment
- blood and tissue C&S
- serum CK (elevated CK usually means myonecrosis – a late sign)
- plain film x-ray (soft tissue gas may be visualized)
- surgical exploration for debridement of infected tissue

### Treatment
- resuscitation with IV fluids
- emergency surgical debridement to confirm diagnosis and remove necrotic tissue (may require amputation)
- IV antibiotics
  - unknown organism: meropenem or piperacillin/tazobactam + clindamycin IV ± vancomycin if MRSA is considered
  - Type I (polymicrobial): piperacillin/tazobactam + clindamycin IV
  - Type II (monomicrobial): cefazolin (or cloxacillin) + clindamycin IV; with confirmed GAS infection, penicillin G + clindamycin IV
  - with Type II, evaluate for streptococcal toxic shock syndrome and the need for IVIg

# Acquired Oral Lesions

### Etiology
- Infection (e.g. candidiasis, gonococcal infection), HSV
- Malignancy (e.g. adenocarcinoma, leukoplakia)
- Poor oral hygiene (e.g. caries, periodontal disease)
- Trauma (e.g. abuse)
- Toxic ingestion
- Xerostomia (e.g. age, medications)
- Systemic diseases (e.g. lichen planus, Behçet disease)

**Table 13. Comparison between Oral Infection vs Oral Carcinoma**

| | Oral Candidiasis | Oral Squamous Cell Carcinoma |
|---|---|---|
| **Risk Factors** | Antibiotics, chemotherapy, radiation therapy<br>Immunocompromise<br>Age – infants, older adults with dentures | Tobacco use (smoked and smokeless)<br>Betel use<br>Alcohol<br>HPV, especially HPV-16 |
| **Morphology** | Pseudomembranous: confluent, white patches or plaques, can be wiped off with a gauze, exposing an erythematous base<br><br>Atrophic candidiasis: red patches localized mainly to the palate and dorsum of the tongue | A lesion of three or more weeks duration:<br>• Red or red and white lesion<br>• Ulcer<br>• Lump<br>• Especially when in combination or if indurated (firm on palpation) |
| **Diagnosis** | Medical and physical | Biopsy and histopathologic examination |
| **Treatment** | Topical antifungal | Referral to ENT |

# Gastrointestinal Infections

- see Gastroenterology, G15 and Pediatrics, P37

# Traveller's Diarrhea

- see Gastroenterology, G18

# Chronic Diarrhea

- see Gastroenterology, G19

# Peptic Ulcer Disease (*H. pylori*)

- see Gastroenterology, G11

# Bone and Joint Infections

## Septic Arthritis

### Definition
- infection of one of more joints by pathogenic microbes

**Medical Emergency**
Septic arthritis is a medical emergency! If untreated, rapid joint destruction will occur

### Routes of Infection
- hematogenous
  - contiguous osteomyelitis common in children
- direct inoculation via skin/trauma
- iatrogenic (surgery, arthroscopy, arthrocentesis)

### Etiology
- gonococcal
  - *N. gonorrhoeae*: previously accounted for 75% of septic arthritis in young sexually active adults
- non-gonococcal
  - *S. aureus*: affects all ages, rapidly destructive, accounts for most non-gonococcal cases of septic arthritis in adults (especially in those with rheumatoid arthritis)
  - *Streptococcus* species (Group A and B)

**Disseminated Gonococcal Infection Triad**
- Migratory arthralgias
- Tenosynovitis next to inflamed joint
- Pustular skin lesions

  - Gram-negatives: affect neonates, elderly, injection drug users, immunocompromised
  - *S. pneumoniae*: affects children
  - *Kingella kingae*: affects children aged <4 yr of age
  - *Haemophilus influenzae* type B (Hib) now rare due to Hib vaccine: consider in unvaccinated children
  - *Salmonella* spp.: characteristic of sickle cell disease
  - coagulase-negative *Staphylococcus* species: prosthetic joints
- if culture negative: partially-treated infection (prior to oral antibiotics), reactive arthritis, rheumatic fever, less common bacterial causes such as *Borrelia* spp. (Lyme disease) or *Tropheryma whipplei* (Whipple's disease), and non-infectious causes

### Risk Factors
- gonococcal
  - age (<40 yr), multiple partners, unprotected intercourse, MSM
- non-gonoccocal
  - most affected children are previously healthy with no risk factors: occasionally preceding history of minor trauma
  - bacteremia (extra-articular infection with hematogenous seeding, endocarditis)
  - prosthetic joints/recent joint surgery
  - underlying joint disease (rheumatoid arthritis, osteoarthritis)
  - immunocompromise (DM, chronic kidney disease, alcoholism, cirrhosis)
  - loss of skin integrity (cutaneous ulcer, skin infection)
  - age >80 yr

### Clinical Feature of Gonococcal Arthritis
- two forms (although often overlap):
  - septic arthritis form- local symptoms in involved joint (swelling, warmth, pain, inability to weight bear, decreased ROM)
  - bacteremic form- systemic symptoms of fever, malaise, chills

### Clinical Feature of Non-Gonoccocal Arthritis
- acute onset of pain, swelling, warmth, decreased range of motion ± fever and chills; in children, refusal to weight bear
- most often in large weight-bearing joints (knee, hip, ankle) and wrists
- usually monoarticular (polyarticular risk factors: rheumatoid arthritis, endocarditis, GBS)

### Investigations
- consider rheumatologic causes for monoarthritis (see Rheumatology, RH3)
- gonococcal: blood C&S, as well as endocervical, urethral, rectal, and oropharyngeal testing
- non-gonococcal: blood C&S
- arthrocentesis (synovial fluid analysis) is mandatory: CBC and differential, Gram stain, C&S, examine for crystals
  - infectious = opaque, increased WBCs (>15,000/mm$^3$: likelihood of infection increases with increasing WBCs), PMNs >90%, culture positive
  - growth of *N. gonorrhoeae* from synovial fluid is successful in <50% of cases
- ± plain x-ray: assess for osteomyelitis, provides baseline to monitor treatment



Intra-articular steroids are contraindicated until septic arthritis has been excluded

### Treatment
- medical
  - empiric IV antibiotics: specific choice depends on clinical scenario and local guidelines; for most adults, cefazolin ± vancomycin is reasonable; for fully vaccinated children, cefazolin or cloxacillin IV unless MRSA is a consideration – delay may result in joint destruction
  - Gram stain and cultures guide subsequent treatment
  - gonococcal: ceftriaxone (+ azithromycin for concurrent treatment of *C. trachomatis*), 7 d of therapy usually sufficient
  - non-gonococcal: antibiotics against *Streptococcus* spp. (2-3 wk IV f/b PO), S. aureus (4 wk IV minimum), or GNB (4 wk, newer evidence suggest early switch to PO is safe and effective)
- surgical intervention if (see Orthopedic Surgery, OR11)
  - would consider surgical intervention on all cases of septic arthritis if possible
  - persistent positive joint cultures on repeat arthrocentesis
  - hip joint involvement, especially in pediatric population
  - prosthetic joint
  - daily joint aspirations until culture sterile
  - physiotherapy

### Prognosis
- gonococcal: responds well after 24-48 h of initiating antibiotics (usually complete recovery)
- non-gonococcal: in children, generally good outcome if treated promptly; in adults, up to 50% morbidity (decreased joint function/mobility)

# Diabetic Foot Infections

### Etiology
- neuropathy, peripheral vascular disease, and hyperglycemia contribute to foot ulcers that heal poorly, and are predisposed to infection
- organisms in mild infection: *Streptococcus* spp., *S. aureus*
- organisms in moderate/severe infection: polymicrobial with aerobes *(S. aureus, Streptococcus, Enterococcus*, GNB) and anaerobes (*Peptostreptococcus, Bacteroides, Clostridium*)

### Clinical Feature
- not all ulcers are infected
- consider infection if: probe to bone (see below), ulcer present >30 d, recurrent ulcers, trauma, PVD, prior amputation, loss of protective sensation, renal disease, or history of walking barefoot
- diagnosis of infected ulcer: ≥2 of the cardinal signs of inflammation (redness, warmth, swelling, pain) OR the presence of pus
- ± crepitus, osteomyelitis, systemic toxicity
- visible bone or probe to bone → osteomyelitis
- infection severity
  - mild = superficial (no bone/joint involvement)
  - moderate = deep (beneath superficial fascia, involving bone/joint) or erythema >2 cm
  - severe = infection in a patient with systemic toxicity (fever, tachypnea, leukocytosis, tachycardia, hypotension)

### Investigations
- curettage specimen from ulcer base, aspirate from an abscess or bone biopsy (results from superficial swabs do not represent organisms responsible for deeper infection)
- blood C&S if febrile
- assess for osteomyelitis by x-ray (although not sensitive in early stages) or MRI/bone scan if high clinical suspicion
  - if initial x-ray normal, repeat 2-4 wk after initiating treatment to increase test sensitivity

### Treatment
- mild to moderate: cefazolin or cephalexin
- severe: options include- 1. ceftriaxone + metronidazole; 2. piperacillin/tazobactam ± vancomycin; 3. meropenem ± vancomycin
- optimize glycemic control, pressure offloading, wound care, consider revascularization

This is empiric treatment, and specific treatment needs to be adjusted based on culture and response to therapy

**Does this Patient with Diabetes have Osteomyelitis of the Lower Extremity?**
JAMA 2008;299:806-813
**Study**: Systematic literature review. 21 studies.
**Population**: 1027 adult patients with DM being investigated for osteomyelitis.
**Intervention**: Various aspects of history, physical exam, laboratory tests, and diagnostic imaging studies versus bone biopsy.
**Primary Outcome**: Diagnostic utility.
**Results**: No studies examined any part of history taking. Temperature, ulcer characteristics (erythema, swelling, purulence), elevated WBC, skin swabs, and soft tissue cultures were not useful. Nuclear imaging has poor specificity for osteomyelitis (62%-88.5%), and MRIs have greater accuracy in detecting osteomyelitis.

# Osteomyelitis

- see Orthopedic Surgery, OR10

# Cardiac Infections

## Infective Endocarditis

### Definition
- infection of cardiac endothelium, most commonly the valves
- classifications: acute vs. subacute, native valve vs. prosthetic valve, right sided vs. left sided
- leaflet vegetations are made of platelet-fibrin thrombi, WBCs, and bacteria

### Risk Factors and Etiology
- predisposing conditions
  - high risk: prosthetic cardiac valve, previous IE, congenital heart disease (unrepaired, repaired within 6 mo, repaired with defects), cardiac transplant with valve disease (surgically constructed systemic-to-pulmonary shunts or conduits)
  - moderate risk: other congenital cardiac defects, acquired valvular dysfunction, hypertrophic cardiomyopathy
  - low/no risk: secundum ASD or surgically repaired ASD < VSD, PDA, MV prolapse, ischemic heart disease, previous CABG
  - opportunity for bacteremia: IVDU, indwelling venous catheter, hemodialysis, poor dentition, DM, HIV
- frequency of valve involvement MV >> AV > TV > PV
  - but in 50% of IVDU-related IE the tricuspid valve is involved

**Table 14. Microbial Etiology of Infective Endocarditis Based on Risk Factors**

| Native Valve | Intravenous Drug Users (IVDU) | Prosthetic Valve (recent surgery <2 mo) | Prosthetic Valve (remote surgery >2 mo) |
|---|---|---|---|
| ***Streptococcus*[1] (36%)** | ***S. aureus* (68%)** | ***S. aureus* (36%)** | ***Streptococcus* (20%)** |
| ***S. aureus* (28%)** | ***Streptococcus* (13%)** | ***S. epidermidis* (17%)** | ***S. aureus* (20%)** |
| ***Enterococcus* (11%)** | *Enterococcus* | Other | ***S. epidermidis* (20%)** |
| *S. epidermidis* | GNB | *Enterococcus* | ***Enterococcus* (13%)** |
| GNB | *Candida* | GNB | Other[2] |
| Other[2] | Other[3] | Other[2] | |

Organisms in bold are the most common isolates
1. *Streptococcus* includes mainly viridans group streptococci
2. Other includes less common organisms such as:
   - *Streptococcus gallolyticus* (previously known as *S. bovis*; usually associated with underlying GI malignancy, cirrhosis)
   - Culture-negative organisms including nutritionally-deficient streptococci, HACEK, *Bartonella, Coxiella, Chlamydia, Legionella, Brucella*
   - *Candida*
3. IVDU endocarditis pathogens depend on substance used to dilute the drugs (i.e. tap water = *Pseudomonas*, saliva = oral flora, toilet water = GI flora)

## Clinical Feature

- systemic
  - fever (80-90%), chills, weakness, rigors, night sweats, weight loss, anorexia
- cardiac
  - dyspnea, chest pain, clubbing (subacute)
  - regurgitant murmur (new onset or increased intensity)
  - signs of CHF (secondary to acute MR, AR)
- embolic/vascular
  - petechiae over legs, splinter hemorrhages (linear, reddish-brown lesion within nail bed)
  - Janeway lesions (painless, 5 mm, erythematous, hemorrhagic pustular lesions on soles/palms)
  - focal neurological signs (CNS emboli), headache (mycotic aneurysm)
  - splenomegaly (subacute)
  - microscopic hematuria, flank pain (renal emboli) ± active sediment
- immune complex
  - Osler's nodes (painful, raised, red/brown, 3-15 mm on digits)
  - glomerulonephritis
  - arthritis
  - Roth's spots (retinal hemorrhage with pale centre)

**Clinical Features of Infective Endocarditis**

**FROM JANE**
**F**ever
**R**oth's spots
**O**sler's nodes
**M**urmur
**J**aneway lesions
**A**nemia
**N**ail-bed hemorrhages (i.e. splinter hemorrhages)
**E**mboli

## Diagnosis

- Modified Duke Criteria
  - definitive diagnosis if: 2 major, OR 1 major + 3 minor, OR 5 minor
  - possible diagnosis if: 1 major + 1 minor, OR 3 minor

**Table 15. Modified Duke Criteria**

| Major Criteria (2) |
|---|
| 1. Positive blood cultures for IE<br>• Typical microorganisms for IE from 2 separate blood cultures (*Streptococcus viridans*, HACEK group, *Streptococcus gallolyticus* (previously known as *S. bovis*), *Staphylococcus aureus*, community-acquired enterococci) OR<br>• Persistently positive blood culture, defined as recovery of a microorganism consistent with IE from blood drawn >12 h apart OR<br>• All of 3 or a majority of 4 or more separate blood cultures, with first and last drawn >1 h apart OR<br>• Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer >1:800<br>2. Evidence of endocardial involvement<br>• Positive echocardiogram for IE (oscillating intracardiac mass on valve or supporting structures, or in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation OR abscess OR new partial dehiscence of prosthetic valve); and new valvular regurgitation (insufficient if increase or change in preexisting murmur) |
| **Minor Criteria (5)** |
| 1. Predisposing condition (abnormal heart valve, IVDU)<br>2. Fever (38.0°C/100.4°F)<br>3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysms, ICH, conjunctival hemorrhages, Janeway lesions<br>4. Immunologic phenomena: glomerulonephritis, rheumatoid factor, Osler's nodes, Roth's spots<br>5. Positive blood culture but not meeting major criteria OR serologic evidence of active infection with organism consistent with IE |

## Investigations

- serial blood cultures: 3 sets (each containing one aerobic and one anaerobic sample) collected from different sites >1 h apart
  - persistent bacteremia is the hallmark of endovascular infection (such as IE)
- repeat blood cultures (at least 2 sets) after 48-72 h of appropriate antibiotics to confirm clearance
- blood work: CBC and differential (normochromic, normocytic anemia), ESR (increased), RF (+), urea/Cr
- urinalysis (proteinuria, hematuria, red cell casts) and urine C&S
- ECG: prolonged PR interval may indicate perivalvular abscess
- echo findings: vegetations, regurgitation, abscess
  - TTE (poor sensitivity) inadequate in 20% (obesity, COPD, chest wall deformities)
  - TEE indicated if TTE is non-diagnostic in patients with at least possible endocarditis or if suspect prosthetic valve endocarditis or complicated endocarditis (e.g. paravalvular abscess/perforation) (~90% sensitivity)

**TEE** transesophageal echo
**TTE** transthoracic echo

### Treatment
- medical
  - usually non-urgent and can wait for confirmation of etiology before initiating treatment unless patient is septic
  - empiric antibiotic therapy if patient is unstable; administer ONLY after blood cultures have been taken. Generally, *S. aureus*, coagulase-negative staphylococcus (CNST), and Gram-negative coverage is important
    - first line empiric treatment for native valve: vancomycin + gentamicin OR ceftriaxone
    - first line empiric treatment for prosthetic valve: vancomycin + gentamicin + rifampin
  - targeted antibiotic therapy: antibiotic and duration (usually 4-6 wk) adjusted based on valve, organism, and susceptibilities
  - monitor for complications of IE (e.g. HF, conduction block, new emboli) and complications of antibiotics (e.g. renal disease)
  - post treatment prophylaxis only recommended for high risk individuals listed above with dental procedures that may lead to bleeding OR invasive procedure of the respiratory tract that involves incision or biopsy of the respiratory mucosa, such as tonsillectomy and adenoidectomy OR procedures on infected skin, skin structure, or musculoskeletal tissue
- dental/respiratory: amoxicillin single dose 30-60 min prior; clindamycin if truly penicillin-allergic
- skin/soft tissue: cephalexin single dose 30-60 min prior; clindamycin if truly penicillin-allergic (modify based on etiology of skin/soft tissue infection)
- surgical
  - most common indication is refractory CHF
  - other indications include: valve ring abscess, fungal etiology, valve perforation, unstable prosthesis, ≥2 major emboli, antimicrobial failure (persistently positive blood cultures), mycotic aneurysm, Staphylococci on a prosthetic valve

### Prognosis
- adverse prognostic factors: CHF, prosthetic valve infection, valvular/myocardial abscess, embolization, persistent bacteremia, altered mental status
- mortality: prosthetic valve IE (25-50%), non-IVDU *S. aureus* IE (30-45%), IVDU *S. aureus* or streptococcal IE (10-15%)

# CNS Infections

## Meningitis

- see Pediatrics, P57

### Definition
- inflammation of the meninges

### Etiology

**Table 16. Common Organisms in Meningitis**

| Bacterial | | | Viral | Fungal | Other |
|---|---|---|---|---|---|
| **Age 0-4 wk** | **Age 1-3 mo** | **Age >3 mo** | | | |
| GBS<br>*E. coli*<br>*L. monocytogenes*<br>*Klebsiella* | GBS<br>*E. coli*<br>*S. pneumoniae*<br>*N. meningitidis*<br>*H. influenzae* | *S. pneumoniae*<br>*N. meningitidis*<br>*L. monocytogenes*<br>(age >50 and comorbidities) | HSV-1, 2<br>VZV<br>Enteroviruses<br>Parechoviruses<br>West Nile | *Cryptococcus*<br>*Coccidioides* | Lyme disease<br>Neurosyphilis<br>TB |

### Risk Factors
- lack of immunization against *H. influenzae* type b, *S. pneumoniae*, and *N. meningitidis* in children
- most cases of bacterial meningitis are due to hematogenous spread from a mucosal surface (nasopharynx)
- direct extension from a parameningeal focus (otitis media, sinusitis) less common
- penetrating head trauma or iatrogenic
- anatomical meningeal defects – CSF leaks
- immunodeficiency (corticosteroids, HIV, asplenia, hypogammaglobulinemia, complement deficiency)
- contact with colonized or infected persons

### Clinical Feature
- neonates and children: fever, lethargy, irritability, vomiting, poor feeding
- older children and adults: fever, headache, neck stiffness, confusion, lethargy, altered level of consciousness, seizures, focal neurological signs, nausea/vomiting, photophobia, papilledema
- petechial rash in meningococcal meningitis (purpura fulminans), seen more frequently on trunk or lower extremities

**Corticosteroids for Acute Bacterial Meningitis**
Cochrane DB Syst Rev 2015;CD004405
**Objectives**: To examine the effect of adjuvant corticosteroid therapy vs. placebo on mortality, hearing loss, and neurological sequelae with acute bacterial meningitis.
**Methods**: RCTs of corticosteroids for acute bacterial meningitis.
**Results**: 25 studies, 4121 participants. Corticosteroids were associated with non-significant mortality reductions (RR 0.90, 95% CI 0.80-1.01). Corticosteroids were associated with lower rates of hearing loss (RR 0.74, 95% CI 0.63-0.87) and neurological sequelae (RR 0.83, 95% CI 0.69-1.00). Corticosteroids were associated with increase in recurrent fever (RR 1.27, 95% CI 1.09-1.47).
**Conclusions**: Corticosteroids significantly reduced hearing loss and neurological sequelae, but did not reduce mortality. Data supports use in high-income countries but no benefit in low-income countries.

**Brudzinski's Sign**
Passive neck flexion causes involuntary flexion of hips and knees

**Kernig's Sign**
Resistance to knee extension when hip is flexed to 90°

**Jolt Accentuation of headache**
Headache worsens when head turned horizontally at 2-3 rotations; more sensitive than Brudzinski's and Kernig's

### Investigations
- blood work: CBC and differential, electrolytes (for SIADH), blood C&S
  - CSF: opening pressure, cell count + differential, glucose, protein, Gram stain, bacterial C&S
  - AFB, fungal C&S, cryptococcal antigen in immunocompromised patients, subacute illness, suggestive travel history or TB exposure
  - PCR for HSV, VZV, enteroviruses; in infants <6 mo, parechoviruses
  - West Nile virus serology in blood and CSF during summer and early fall if viral cause suspected
- imaging/neurologic studies: CT, MRI, EEG if focal neurological signs present

**Table 17. Typical CSF Profiles for Meningitis**

| CSF Analysis | Bacterial | Viral |
|---|---|---|
| **Glucose (mmol/L)** | Decreased | Normal |
| **Protein (g/L)** | Markedly Increased | Increased |
| **WBC** | 500-10,000/μL | 10-500/μL |
| **Predominant WBC** | Neutrophils | Lymphocytes |

### Treatment
- bacterial meningitis is a medical emergency: do not delay antibiotics for CT or LP
- empiric antibiotic therapy
  - age ≤28 d: ampicillin + cefotaxime
  - age 29 d-3 mo: cefotaxime + vancomycin
  - age >3 mo: ceftriaxone + vancomycin
    - add ampicillin IV if risk factors for infection with *L. monocytogenes* present: age >50, alcoholism, immunocompromised
- steroids in acute bacterial meningitis: dexamethasone IV within 20 min prior to or with first dose of antibiotics
  - continue in those patients with proven pneumococcal meningitis
  - not recommended for patients with suspected bacterial meningitis in some resource-limited countries
  - not recommended for neonatal meningitis

### Prevention
- see Pediatrics, P4
- immunization
  - children: immunization against *H. influenzae* type B (Pentacel®), *S. pneumoniae* (Synflorix®, Prevnar-13®), *N. meningitidis* (Menjugate®, Menactra®, Nimenrix®, Menveo®, Bexsero®)
  - adults: immunization against *N. meningitidis* in selected circumstances (outbreaks, travel, epidemics) and *S. pneumoniae* (Pneumovax®) for high-risk groups
- prophylaxis: close contacts of patients infected with *H. influenzae* type B should be treated with rifampin if they live with an inadequately immunized (<4 yr) or immunocompromised child (<18 yr); ciprofloxacin, rifampin, or ceftriaxone if close or household contact of a patient with *N. meningitidis*; meningococcal vaccines are also recommended for post-exposure prophylaxis for close contacts and in outbreak control

### Prognosis
- complications
  - death, headache, seizures, cerebral edema, hydrocephalus, SIADH, residual neurological deficit (especially CN VIII), deafness
- mortality
  - *S. pneumoniae* 25%; *N. meningitidis* 5-10%; *H. influenzae* 5%
  - worse prognosis if: extremes of age, delays in diagnosis and treatment, stupor or coma, seizures, focal neurological signs, septic shock at presentation

## Encephalitis

### Definition
- inflammation of the brain parenchyma

### Etiology
- identified in only 40-70% of cases
  - when cause is identified, the most common etiology is viral: HSV, VZV, EBV, CMV, enteroviruses, parechoviruses, West Nile and other arboviruses, influenza and other respiratory viruses, HIV, mumps, measles, rabies, polio
  - bacteria: *L. monocytogenes*, *mycobacteria*, spirochetes (Lyme, syphillis), *Mycoplasma pneumoniae*
  - parasites: protozoa (e.g. *Toxoplasma*) and helminths (rare)
  - fungi: e.g. *Cryptococcus*
  - post-infectious (e.g. acute disseminated encephalomyelitis [ADEM])
  - auto-antibody mediated encephalitis
    - anti-N-methyl-D-aspartate (NMDA) receptor encephalitis most common
    - in adults, most autoantibody-mediated encephalitis cases are associated with malignancy

**CSF Gram Stain Findings**
- *S. pneumoniae* – GP diplococci
- *N. meningitidis* – GN diplococci
- *H. influenzae* – Pleiomorphic GN coccobacilli
- *L. monocytogenes* – GP rods

**Does this Adult Patient Have Acute Meningitis? From The Rational Clinical Examination**
JAMA 2009; http://www.jamaevidence.com/content/3482857
**Study**: Systematic review of articles assessing the sensitivity and specificity of clinical exam maneuvers for the diagnosis of adult meningitis.
**Results**: In retrospective studies, sensitivity for headache was 68%, and 52% for nausea and vomiting. Sensitivity for physical exam findings is similarly low (fever: 87%, neck stiffness: 80%, altered mental status: 69%). Sensitivity for the combination of the classic triad of fever, neck stiffness, and altered mental status was 46%. In prospective studies, sensitivity of headache was 92%, while sensitivity of nausea/vomiting could not be pooled, and ranged from 32-70%. Brudzinski's and Kernig's signs had a sensitivity of 5% and Kernig's sign only 5-9%. Jolt accentuation had a sensitivity of 97%.
**Conclusions**: Data were heterogeneous, and lacked standardization of clinical exams. No single item on clinical history or physical exam was sufficient to rule out meningitis, including Kernig's and Brudzinski's signs, or the absence of the classic triad of fever, neck stiffness, and altered mental status meningitis. Jolt accentuation has high sensitivity, but further research is needed. LP may be performed safely without CT head in patients without altered LOC, no recent seizure, no history of CNS disease, not immunocompromised, and <60 yr.

**Public Health Agency of Canada Indications for Adult Immunization**

**Pneumococcal Polysaccharide Vaccine (i.e. Pneumovax®)**
- >65 yr (option to also give pneumococcal conjugate vaccine; if so, to give polysaccharid vaccine 8 wk after conjugate vaccine)

**Pneumococcal Polysaccharide Vaccine (i.e. Pneumovax®) and Pneumococcal Conjugate Vaccine**
- Chronic cardiovascular/respiratory/hepatic/renal disorders, asplenia, sickle cell, or immunosuppression (polysaccharide vaccine to be given 8 wk after pneumococcal conjugate vaccine)

**Meningococcal Quadrivalent Vaccine (Menactra® or Menomune®)**
- Healthy young adults
- Asplenia
- Travellers to high-risk areas
- Military recruits or laboratory personnel
- Complement, factor D, or properdin deficiency or acquired terminal complement deficiency through receipt of eculizumab

**Multicomponent Meningococcal Serogroup B Vaccine (Bexsero®)**
- Asplenia
- Military recruits or laboratory personnel
- Complement, factor D, or properdin deficiency, or acquired terminal complement deficiency through receipt of eculizumab

### Pathophysiology
- acute inflammatory disease of the brain due to direct invasion or pathogen-initiated immune response
- viruses may reach the CNS via peripheral nerves (e.g. rabies, HSV)
- herpes simplex encephalitis
  - acute, necrotizing, asymmetrical hemorrhagic process with lymphocytic and plasma cell reaction which usually involves the medial temporal and inferior frontal lobes
  - associated with HSV-1, less likely caused by HSV-2
- influenza and other respiratory viruses are associated with acute necrotizing encephalopathy (ANE); likely mediated by pathogen-initiated immune response

### Clinical Feature
- constitutional: fever, chills, malaise, nausea/vomiting
- meningeal involvement (meningoencephalitis): headache, nuchal rigidity
- parenchymal involvement: seizures, altered mental status, focal neurological signs
- herpes simplex encephalitis
  - acute onset (<1 wk) of focal neurological signs: hemiparesis, ataxia, aphasia, focal or generalized seizures
  - temporal lobe involvement: behavioural disturbance
  - usually rapidly progressive over several days and may result in coma or death
  - common sequelae: memory and behavioural disturbances
  - rare complication: development of encephalopathy and Kluver-Bucy syndrome characteristics 1 mo after completion of treatment for HSV encephalopathy

### Investigations
- CSF: opening pressure, cell count and differential, glucose, protein, Gram stain, bacterial C&S, PCR for HSV, VZV, EBV, enteroviruses/parechoviruses, M. *pneumoniae*, and selectively for other less common etiologies
- serology: may aid diagnosis of certain causes of encephalitis (e.g. EBV, West Nile virus, rabies, *Bartonella henselae*)
- imaging/neurologic studies: CT, MRI, EEG to define anatomical sites affected
- invasive testing: brain tissue biopsy may be required for culture, histological examination, and immunocytochemistry (if diagnosis not clear via non-invasive means)
- findings in herpes simplex encephalitis (must rule out due to high mortality)
  - CT/MRI: medial temporal lobe necrosis
  - EEG: early focal slowing, periodic discharges

### Treatment
- general supportive care
- monitor vital signs carefully
- IV acyclovir empirically until HSV encephalitis ruled out



Meningitis and encephalitis patients can be distinguished based on their cerebral function. Cerebral function is abnormal in encephalitis patients (e.g. altered mental status, motor or sensory deficits, altered behaviour, speech or movement disorders), but may be normal in patients with meningitis. Note however, that there is considerable overlap between the two syndromes ("meningoencephalitis")



**Bortezomib for Treatment of Therapy-Refractory anti-NMDA Receptor Encephalitis**
Neurology 2017;88(4):366-70.
**Objective**: To assess therapeutic potential of the plasma-cell-depleting proteasome inhibitor bortezomib in severe and therapy-refractor cases of anti-NMDA receptor encephalitis.
**Methods**: 5 severely affected patients with anti-NMDA receptor encephalitis with delayed treatment response or resistance to standard immunosuppressive and B-cell-depleting drugs were treated with 1-6 cycles of 1.3 mg/m2 bortezomib. Monitored for adverse events.
**Results**: 4 out of 5 patients showed clinical improvement or disease remission, accompanied by decline of anti-NMDA receptor antibodies. Associated with acceptable safety profile.
**Conclusions**: Bortezomib may be a promising escalation therapy in patients with severe and therapy-refractor anti-NMDA receptor encephalitis (Class IV evidence).

## Generalized Tetanus

- see Pediatrics, P4

### Etiology and Pathophysiology
- caused by *Clostridium* tetani: motile, spore forming, anaerobic Gram-positive *bacillus*
- found in soil, splinters, rusty nails, GI tract (humans and animals)
- traumatic implantation of spores into tissues with low oxygenation (e.g. puncture wounds, burns, nonsterile surgeries or deliveries)
- upon inoculation, spores transform into *C. tetani* bacilli that produce tetanus toxin
  - toxin travels via retrograde axonal transport to the CNS where it irreversibly binds presynaptic neurons to prevent the release of inhibitory neurotransmitters (e.g. GABA)
  - net effect is the disinhibition of spinal motor reflexes which results in tetany and autonomic hyperactivity

### Clinical Feature
- generalized tetanus
  - initially present with painful spasms of masseters (trismus or "lockjaw")
  - sustained contraction of skeletal muscle with periodic painful muscle spasms (triggered by sensory stimuli, e.g. loud noises)
  - paralysis descends to involve large muscle groups (neck, abdomen)
  - apnea, respiratory failure, and death secondary to tonic contraction of pharyngeal and respiratory muscles
- autonomic hyperactivity
  - diaphoresis, tachycardia, HTN, fever as illness progresses

### Investigations
- primarily a clinical diagnosis, often although not always with a history of a traumatic wound and lack of immunization
- culture wounds, creatine kinase (CK) may be elevated

### Treatment

- stop toxin production
  - wound debridement to clear necrotic tissue and spores
  - antimicrobial therapy: IV metronidazole; IV penicillin G is an effective alternative
- neutralize unbound toxin with tetanus immune globulin (TIg)
- supportive therapy: intubation, spasmolytic medications (benzodiazepines), quiet environment, cooling blanket
- control autonomic dysfunction: α- and β-blockade (e.g. labetalol), magnesium sulfate



Antimicrobial therapy (e.g. metronidazole) may fail to treat *C. tetani* unless adequate wound debridement is performed

### Prevention

- infection with *C. tetani* does not produce immunity – vaccinate patients on diagnosis
- tetanus toxoid vaccination (see Pediatrics, P4 and Emergency Medicine, ER17)

## Rabies

### Definition

- acute progressive encephalitis caused by RNA virus (genus *Lyssavirus* of the Rhabdoviridae family)

### Etiology and Pathophysiology

- any mammal can transmit the rabies virus
  - most commonly transmitted by raccoon, skunk, bat, fox, cat, and dog; monkeys also a risk in the developing world
- transmission: breaching of skin by teeth or direct contact of infectious tissue (saliva, neural tissue) with skin or mucous membranes
  - almost all cases due to bites
  - animals can be carriers for several days before manifest signs of disease
- virus travels via retrograde axonal transport from PNS to CNS
- virus multiplies rapidly in brain, then spreads to other organs, including salivary glands
- development of clinical signs occurs simultaneously with excretion of rabies virus in saliva
  - infected animal can transmit rabies virus as soon as it shows signs of disease

### Clinical Feature

- five stages of disease

1. incubation period
   - 1-3 mo on average (can range from days to years)
2. prodrome (<1 wk)
   - low-grade fever, malaise, anorexia, nausea/vomiting, headache, sore throat
   - pain, pruritus, and paresthesia may occur at wound site
   - once prodromal symptoms develop, there is rapid, irreversible progression to death
     - progression from prodrome to coma and death may occur without an intervening acute neurologic syndrome
3. acute neurologic syndrome: 2 types (<1 wk)
   a. encephalitic (most common): hyperactivity, fluctuating LOC, hydrophobia, aerophobia, hypersalivation, fever, seizures
     - painful pharyngeal spasms on encountering gust of air or swallowing water cause aerophobia and hydrophobia, respectively

   b. paralytic: quadriplegia, loss of anal sphincter tone, fever
4. coma
   - complete flaccid paralysis, respiratory, and cardiovascular failure
5. death (within days to weeks of initial symptoms)

### Investigations

- purpose of diagnosis by investigations is to limit patient contact with others and to identify others exposed to the infectious source
- ante-mortem: direct immunofluorescence or PCR on multiple specimens: saliva, skin biopsy, serum, CSF
- post-mortem: direct immunofluorescence in nerve tissue, presence of Negri bodies (inclusion bodies in neurons)

### Treatment

- post-exposure prophylaxis depends on regional prevalence and circumstances surrounding injury
- mandatory to report animal bite/contact that may result in rabies to Public Health Authority
- if not previously immunized:
  - wound care: clean wound promptly and thoroughly with soap and running water
  - passive immunization: rabies immunoglobulin (RIG) infiltrated into wound site, with any remaining volume administered IM in anatomical site distant from vaccine administration. Due to variable response rates, vaccine should not be administered into gluteal muscle
  - active immunization: inactivated human diploid cell rabies virus vaccine (HDCV) – series of 4 shots post-exposure on days 0, 3, 7 and 14. Vaccine administered into deltoid

- if previously immunized:
  - wound care: clean wound promptly and thoroughly with soap and running water
  - two doses of HDCV into deltoid on days 0 and 3
  - no RIG administered
- treatment is supportive once victim manifests signs and symptoms of disease

### Prevention
- pre-exposure vaccination
  - recommended for high risk persons: laboratory staff working with rabies, veterinarians, animal and wildlife control workers, long-term travellers to endemic areas

# Systemic Infections

## Sepsis and Septic Shock

- see Respirology, R30

### Definitions
- bacteremia: bacteria in blood from primary bloodstream infection or secondary to infection of another body system
- sepsis: severe organ dysfunction resulting from dysregulated host response to infection
  - organ dysfunction identified via acute change in SOFA score >2 points
  - qSOFA score used initially to screen patients for suspected sepsis using three criteria:
    1. respiratory rate >22/min
    2. systolic BP <100 mmHg
    3. altered mentation (GCS <15)
- septic shock: subset of sepsis with circulatory and cellular/metabolic dysfunction; clinically defined in cases where despite adequate volume resuscitation there is both:
  1. persistent hypotension requiring vasopressors to maintain MAP >65 mmHg AND
  2. serum lactate >2 mmol/L

SOFA score >2 = 10% mortality risk in patient with suspected infection
Hospital mortality with septic shock >40%

**qSOFA score**
1. respiratory rate >22/min
2. systolic BP <100 mmHg
3. altered mentation (GCS <15)

### Pathophysiology
- causative agents are identified in only 50-70% of cases
- when organisms are identified, Gram-positive and Gram-negative organisms are the cause in 90% of cases
- bacteremia → local immune response → pro-inflammatory cytokine release → spread of immune response beyond local environment → unregulated, exaggerated systemic immune response → vasodilation and hypotension → distributive shock and reduced $O_2$ delivery to tissues → anaerobic metabolism and lactic acid production → metabolic acidosis → multiple organ failure

### Clinical Feature
- history: symptoms and signs specific to an infectious source- e.g. cough, headache, dysuria, purulent exudate, rash
- general symptoms of infection: fever, chills, pain, dyspnea, cool extremities, fatigue, malaise, anxiety, confusion
- physical: abnormal vitals (e.g. fever, tachypnea, tachycardia, hypotension), flushed skin, altered mental status, local signs of infection(e.g. pharyngitis, septic arthritis, neck stiffness, skin wounds/ulcers, or murmurs)

**The Third International Consensus**
Definitions for Sepsis and Septic Shock (Sepsis-3) in 2016 re-defined sepsis using the Sequential Organ Failure Assessment (SOFA) score for diagnosis and Quick-SOFA (qSOFA) for screening of end-organ failure. The terms severe sepsis and systemic response inflammatory response syndrome (SIRS) are no longer part of the sepsis definition.

### Investigations
- CBC and differential, electrolytes, urea, creatinine, liver enzymes, ABG, lactate, INR, PTT, troponin, blood C&S x2, urinalysis, urine C&S, and cultures of any wounds or lines
- CXR (other imaging depends on suspicion of focus of infection)
- nasopharyngeal swab/stool/sputum cultures, throat swabs, genital swab, LP as indicated

### Treatment (see Respirology, R30)
- respiratory support: $O_2$ ± intubation
- cardiovascular support: IV fluids ± blood transfusion + vasopressors + ICU
- IV antibiotics (empirical, depends on suspected source)
  - start with broad spectrum antibiotics (e.g. piperacillin/tazobactam or meropenem) ± additional agents depending on patient risk factors, suspected etiology of infection, and local microbial susceptibilities (± aminoglycoside for drug-resistant Gram-negatives or vancomycin for MRSA)
  - narrow once susceptibilities are known
- source control: procedure to control focus of infection (catheter removal, abscess drainage)
- hydrocortisone IV in patients with septic shock unresponsive to fluid resuscitation and vasopressors

# Leprosy (Hansen's Disease)

### Etiology
- *Mycobacterium leprae*: obligate intracellular bacteria, slow-growing (doubling time 12.5 d), survives in macrophages
- bacteria transmitted from nasal secretions, potentially via skin lesions
- invades skin and peripheral nerves leading to chronic granulomatous disease

### Clinical Feature
- lesions involve cooler body tissues (e.g. skin, superficial nerves, nose, eyes, larynx)
- spectrum of disease determined by host immune response to infection
  - i. paucibacillary "tuberculoid" leprosy (intact cell-mediated immune response)
    - ≤5 hypoesthetic lesions, usually hypopigmented, well-defined, dry
    - early nerve involvement, enlarged peripheral nerves, neuropathic pain
    - may be self-limited, stable, or progress over time to multibacillary "lepromatous" form
  - ii. multibacillary "lepromatous" leprosy (weak cell-mediated immune response)
    - ≥6 lesions, symmetrical distribution
    - leonine facies (nodular facial lesions, loss of eyebrows, thickened ear lobes)
    - extensive cutaneous involvement, late and insidious nerve involvement causing sensory loss at the face and extremities
  - iii. borderline leprosy
    - lesions and progression lies between tuberculoid and lepromatous forms

### Investigations
- skin biopsy down to fat or slit skin smears for AFB staining, PCR
- histologic appearance: intracellular bacilli in spherical masses (lepra cells), granulomas involving cutaneous nerves

### Treatment (WHO Treatment Regimens)
- paucibacillary: dapsone daily + rifampin monthly x 6 mo
- single skin lesion paucibacillary: single dose of rifampicin, ofloxacin, and minocycline
- multibacillary: dapsone + rifampin monthly + clofazimine monthly x 12 mo AND low dose clofazimine once daily x 12 mo
- treatment of leprosy can cause an immune reaction to killed or dying bacteria (e.g. erythema nodosum leprosum and reversal reaction): symptomatic management with NSAIDs if mild, prednisone with 6-12 wk taper if severe; thalidomide for erythema nodosum leprosum

### Prognosis
- curable with WHO-approved treatment regimens
- complications: muscle atrophy, contractures, trauma/superinfection of lesions, crippling/loss of limbs, erythema nodosum leprosum, social stigmatization due to clofazimine hyperpigmentation
- long post-treatment follow-up warranted to monitor for relapse and immune reactions

# Lyme Disease





**BAKE a Key Lyme Pie**

**B**ell's palsy
**A**rthritis
**K**ardiac block
**Lyme**
**E**rythema chronicum migrans

### Etiology/Epidemiology
- spirochete bacteria: *Borrelia burgdorferi* (N. America), *B. garinii, B. afzelii* (Europe and Asia)
- transmitted by *Ixodes* tick
- reported in 49 of the 50 U.S. states, but most cases occur in the Northeast, the Midwest, and Northern California
- in Canada, reported in southern and southeastern Quebec, southern and eastern Ontario, southeastern Manitoba, New Brunswick and Nova Scotia, as well as southern British Columbia
- small rodents (mice) serve as primary reservoir, while larger animals (white-tailed deer) serve as hosts for ticks
- human contact usually May-August in fields with low brush near wooded areas
- infection usually requires >36 h tick attachment

### Clinical Feature
- stage 1 (early localized stage: 7-14 d post-bite)
  - malaise, fatigue, headache, myalgias
  - erythema migrans: expanding, non-pruritic bulls-eye (target) lesions (red with clear centre) at site of tick bite
- stage 2 (early disseminated stage: weeks post-infection)
  - CNS: aseptic meningitis, CN palsies (CN VII palsy), peripheral neuritis
  - cardiac: transient heart block or myocarditis
- stage 3 (late persistent stage: months to years post-infection)
  - may not have preceding history of early stage infection
  - MSK: chronic monoarticular or oligoarticular arthritis
  - acrodermatitis chronicum atrophicans (due to *B. afzelii*)
  - neurologic: encephalopathy, meningitis, neuropathy

### Investigations
- order Public Health Lab approved Lyme disease testing and interpret results on basis of symptoms

### Prevention
- use of protective clothing (tuck pants into socks), insect repellent, inspection for ticks and prompt removal of tick
- doxycycline prophylaxis within 72 h of removal of an engorged *Ixodes scapularis* tick in hyperendemic area (local rate of infection of ticks ≥20%) for patients >8 yr who are not pregnant or lactating

### Treatment
- stage 1: doxycycline/amoxicillin/cefuroxime
- stage 2-3: ceftriaxone

## Toxic Shock Syndrome

### Etiology
- superantigens produced by some strains of *S. aureus* or GAS cause widespread T-cell activation and pro-inflammatory cytokine release (IL-1, IL-6, TNF)
- course of disease is precipitous and leads to acute fever, shock, multiorgan failure
- Staphylococcal TSS involves the production of superantigen TSST-1 (toxic shock syndrome toxin 1)
- Streptococcal TSS involves the production of superantigens SPEA, SPEB, SPEC

### Risk Factors
- Staphylococcal: tampon use, nasal packing, wound infections (e.g. postpartum vaginal or Cesarean or other surgical infections)
- Streptococcal: minor trauma, surgical procedures, preceding viral illness (e.g. chickenpox), use of NSAIDs

### Clinical Feature and Investigations
- acute onset
- Staphylococcal TSS
  - T >38.9°C
  - sBP <90 mmHg
  - diffuse erythroderma with subsequent desquamation, especially on palms and soles
  - involvement of 3 or more organ systems: GI (vomiting, diarrhea), muscular (myalgia, increased CK), mucous membranes (hyperemia), renal, hepatic, hematologic (thrombocytopenia), CNS (disorientation)
  - isolation of *S. aureus* is not required for diagnosis (*S. aureus* is rarely recovered from blood in TSS)
- Streptococcal TSS
  - sBP <90 mmHg
  - isolation of GAS from a normally sterile site (e.g. blood, pleural, tissue biopsy, or surgical wound)
  - ≥2 of coagulopathy, liver involvement, ARDS, soft tissue necrosis (necrotizing fasciitis, myositis, gangrene), renal impairment, erythematous macular rash that may desquamate

### Treatment
- supportive care, fluid resuscitation, surgical debridement of infected tissue
- Streptococcal: IV penicillin and clindamycin and ± IVIg
- Staphylococcal: for methicillin-susceptible *S. aureus*: clindamycin + cloxacillin (IV); for MRSA: clindamycin + vancomycin x 10-14 d

## Cat Scratch Disease

### Etiology
- *Bartonella henselae*: intracellular bacteria
- cat-to-human transmission via cat scratch/bite

### Clinical Feature
- skin lesion appears 3-10 d post-inoculation
- may be followed by fever, tender regional lymphadenopathy
- in some patients, organism may disseminate causing fever of unknown origin, hepatosplenomegaly, retinitis, encephalopathy, infective endocarditis, uveitis
- usually self-limited

### Investigations
- serology, PCR, lymph node biopsy

### Treatment
- the disease may be self-limited but treatment is recommended by the Infectious Disease Society of America with a 5 d course of azithromycin for immunocompetent patients with mild to moderate illness
- needle aspiration of painful suppurative lymph nodes may hasten the relief of symptoms
- combination therapy consisting of doxycycline or azithromycin plus rifampin often used for disseminated disease (neuroterinitis, hepatosplenic involvement)

## Rocky Mountain Spotted Fever

### Etiology
- *Rickettsia rickettsii*: obligate intracellular Gram-negative organism
- reservoir hosts: rodents, dogs
- vectors: *Dermacentor* ticks
- organisms cause inflammation of endothelial lining of small blood vessels, leading to small hemorrhages and thrombi
- can cause widespread vasculitis leading to headache, and CNS changes; can progress to death if treatment is delayed

### Clinical Feature
- usually occurs in summer following tick bite
- influenza-like prodrome: acute onset fever, headache, myalgia, nausea/vomiting, anorexia
- macular rash appearing on day 2-4 of fever
  - begins on wrists and ankles, then spreads centrally to arms/legs/trunk/palms/soles
  - occasionally "spotless" (10% of patients)

### Investigations
- skin biopsy and serology (indirect fluorescent antibody test)

### Treatment
- doxycycline, usually 5-7 d (treat for 3 d after defervescence)

## West Nile Virus

### Epidemiology
- virus has been detected throughout the United States and much of southern Canada (Ontario and Manitoba)
- overall case-fatality rates in severe cases is ~10%

### Transmission
- primarily from mosquitoes that have fed on infected birds (crows, blue jays)
- transplacental, blood products (rare), organ transplantation

### Clinical Feature
- 80% are asymptomatic
- most symptomatic cases are mild (West Nile fever): acute onset of headache, back pain, myalgia, anorexia, maculopapular non-pruritic rash involving chest, back, arms
- severe complications: encephalitis, meningoencephalitis, and acute flaccid paralysis (especially in those >60 yr)

### Investigations
- IgM antibody in serum or CSF is the best test (cross reactivity with yellow fever and Japanese encephalitis vaccines, and with dengue fever and St. Louis virus infection); may not reflect current illness as IgM antibody can last for >6 mo
- viral isolation by PCR from CSF, tissue, blood, and fluids (all have low sensitivity)
- CSF: elevated lymphocytes and protein if CNS involvement

### Treatment and Prevention
- treatment: supportive
- prevention: mosquito repellant (DEET, picaridin), drain stagnant water, community mosquito control programs

# Syphilis

## Etiology
- *Treponema pallidum*: thick motile spirochetes historically detectable by dark-field microscopy
- transmitted sexually, vertically, or parenterally (rare)

## Clinical Feature
- see Dermatology, D31 and Gynecology, GY29
- multi-stage disease
  1. primary syphilis (3-90 d post-infection)
     - painless chancre at inoculation site (any mucosal surface)
     - regional lymphadenopathy
     - acute disease lasts 3-6 wk, 25% progress to secondary syphilis without treatment
  2. secondary syphilis = systemic infection (2-8 wk following chancre)
     - maculo-papular non-pruritic rash including palms and soles
     - generalized lymphadenopathy, low grade fever, malaise, headache, aseptic meningitis, ocular/otic syphilis
     - condylomata lata: painless, wart-like lesion on palate, vulva, or scrotum (highly infectious)
  3. latent syphilis
     - asymptomatic infection that follows untreated primary/secondary syphilis
     - early latent (<1 yr post-infection) or late latent/unknown duration (>1 yr post-infection)
     - increased transmission risk with early latent; longer treatment duration required for late latent
  4. tertiary syphilis (1-30 yr post-infection)
     - gummatous syphilis: nodular granulomas of skin, bone, liver, testes, brain
     - aortic aneurysm and aortic insufficiency
     - neurosyphilis: dementia, personality changes, Argyll-Robertson pupils, tabes dorsalis
  5. congenital syphilis
     - causes spontaneous abortions, stillbirths, congenital malformations, developmental delay, deafness
     - most infected newborns are asymptomatic
     - clinical manifestations in early infancy include rhinitis (snuffles), lymphadenopathy, hepatosplenomegaly, pseudoparalysis (bone pain associated with osteitis), and rash (usually maculopapular and involving palms and soles)
     - late onset manifestations (>2 yr of age) include saddle nose, saber shins, Clutton joints, Hutchinson's teeth, mulberry molars, rhagades, CN VIII deafness, interstitial keratitis, juvenile paresis

## Investigations
- syphilis tests are conducted by public health labs. Thus order set for syphilis is simplified and does not require specification of which test to complete. Below are details on what tests are conducted at the public health lab
- screening tests: CMIA, CLIA, EIA (treponemal), RPR, or VDRL (non-treponemal)
- confirmatory tests: TPPA, FTA-ABS, MHA-TP, TPI
- LP for neurosyphilis if: seropositive and symptoms of neurosyphilis or treatment failure/other tertiary symptoms, or with HIV and late latent/unknown duration syphilis; consider in others
- for congenital syphilis, LP is essential; long bone x-rays may also be helpful

## Treatment
- for 1°, 2°, early latent: benzathine penicillin G 2.4 million units IM x 1
- for 3°, late latent: benzathine penicillin G 2.4 million units IM weekly x 3
- if truly allergic to penicillin: doxycycline 100 mg PO bid x 14 d is a second line therapy
- for pregnant patients allergic to penicillin, oral desensitization techniques are considered safe
- neurosyphilis: aqueous Penicillin G 18-24 million units/d IV x 14 d ± single dose of benzathine penicillin
- for congenital syphilis, penicillin G IV x 10 d
- see Family Medicine, FM43 for generalized STI workup





**Argyll Robertson Pupil**
Accommodates but does not react to light



**Those with Untreated 1° or 2° Syphilis**
1/3 cure
1/3 latent indefinitely
1/3 3° syphilis



**Causes of False Positive VDRL and RPR Tests**

**V**iruses (mononucleosis, hepatitis)
**D**rugs and substance abuse
**R**heumatic fever
**L**upus and leprosy



Patients with 2° or 3° syphilis treated with penicillin may experience a Jarisch-Herxheimer reaction. Lysis of organisms release pyrogens thought to cause fever, chills, myalgia, flu-like symptoms may last up to 24 h



| | |
|---|---|
| **VDRL** | Venereal Disease Research Laboratory |
| **RPR** | Rapid Plasma Reagin |
| **EIA** | Enzyme Immunoassay |
| **CLIA** | ChemiLuminescent ImmunoAssay |
| **CMIA** | ChemiLuminescent Microparticle ImmunoAssay |
| **FTA-ABS** | Fluorescent Treponema Antibody-Absorption |
| **MHA-TP** | Microhemagglutination Assay *T. pallidum* |
| **TPPA** | *T. pallidum* Particle Agglutination Assay |
| **TPI** | *T. pallidum* immobilization test |

# Tuberculosis



**Tuberculous Polyserositis**
pleural + pericardial + peritoneal effusions (usually from granuloma breakdown that spills TB into pleural cavity – very rare)

## Etiology, Epidemiology, and Natural History

- 1/3 of the world's population is infected with TB
- contracted by aerosolized inhalation of *Mycobacterium tuberculosis*, a slow growing aerobe (doubling time = 18 h) that can evade innate host defenses, survive, and replicate in macrophages
- inhalation and deposition in the lung can lead to one of the following outcomes
  1. immediate clearance of the pathogen
  2. latent TB: asymptomatic infection contained by host immune defenses (represents 90% of infected people)
  3. primary TB: symptomatic, active disease (represents 5% of infected people)
  4. secondary TB: symptomatic reactivation of previously dormant TB (represents 5-10% of those with latent TB, most often within the first 1-2 yr of initial infection) at a pulmonary or extra-pulmonary site

## Risk Factors

- social and environmental factors
  - travel or birth in a country with high TB prevalence (e.g. Asia, Latin America, Sub-Saharan Africa, Eastern Europe)
  - Aboriginal (particular inuit), the incident of TB is 25 times higher in Canadian-born aboriginal compare to Canadian-born nonaboriginal
  - personal/occupational contact, crowded living conditions, low SES/homeless, IVDU
- host factors
  - immunocompromised/ (especially HIV, including extremes of age)
  - immunosuppressed (TNF**α** inhibitors, glucocorticoids)
  - silicosis
  - chronic kidney disease requiring dialysis
  - diabetes
  - malignancy and chemotherapy
  - substance use (e.g. drug use, alcoholism, smoking)

## Clinical Feature

- primary infection usually asymptomatic, although progressive primary disease may occur, especially in children and immunosuppressed patients
- secondary infection/reactivation usually produces constitutional symptoms (fatigue, anorexia, night sweats, weight loss) and site-dependent symptoms

1. pulmonary TB
   - chronic productive cough ± hemoptysis, fever, night sweats, weight loss, chest pain, anorexia
   - CXR consolidation or cavitation, lymphadenopathy, predominantly upper lung findings but variable
   - non-resolving pneumonia despite standard antimicrobial therapy
2. miliary TB
   - widely disseminated spread especially to lungs, abdominal organs, marrow, CNS
   - CXR: multiple small 2-4 mm millet seed-like lesions throughout lung
3. extra-pulmonary TB
   - can occur in any organ - lymphadenitis, pleurisy, pericarditis, hepatitis, peritonitis, meningitis, osteomyelitis (vertebral = Pott's disease), adrenal (causing Addison disease), renal, ovarian

## Investigations

- screening for latent TB may be done via tuberculin skin test (TST) or IFN-γ release assay (IGRA)
  - both can be used to diagnose prior TB exposure. IGRA has fewer false positives as does not detect antigens in BCG vaccine or most types of non-tuberculosis-Mycobacteria
    - neither should be used for active TB diagnosis or monitoring anti-TB treatment response
    - TST preferred when repeat testing planned to assess risk of new infection (e.g. serial testing in healthcare)
  - IGRA preferred when BCG vaccine after 1 year of age, vaccination more than once, or unable to return for reading
- diagnostic tests/investigations for active pulmonary TB
  - sputum specimens (either spontaneous or induced) should be collected for acid-fast bacilli smear and culture; the three specimens can be collected on the same day, a minimum of 1 hour apart
  - BAL if other lung pathology (e.g. lung cancer) also suspected, or TB suspected despite negative sputum samples
  - CXR
    - classic triad: apical-posterior infiltrates, lung volume loss, cavitation
    - atypical features: hilar/mediastinal lymphadenopathy, non-cavitary infiltrates
    - signs of complications: endobronchial spread, pleural effusion, pneumothorax
    - ghon complex: a parenchymal granuloma, indicating a previous tuberculosis infection, and an involved hilar lymph node on the same side

### Prevention

- primary prevention
  - airborne isolation for active pulmonary disease
  - BCG vaccine
    - ~80% effective against pediatric miliary and meningeal TB
    - effectiveness in adults debated (anywhere from 0-80%)
    - recommended in high-incidence communities in Canada for infants in whom there is no evidence of HIV infection or immunodeficiency; widely used in other countries
- RIF (10 mg/kg [600 mg maximum]) daily for 4 mo
  - INH (5 mg/kg [300 mg maximum]) and RIF (10 mg/kg [600 mg maximum]) daily for 3 mo
  - INH (15 mg/kg [900 mg maximum]) and RPT (dose by weight) weekly for 3 mo
  - INH (5 mg/kg [300 mg maximum]) daily for 6 to 9 mo

### Treatment of Active Infection

- given the nuances of TB treatment, active TB infection should be managed by an experienced TB clinician
- pulmonary TB: INH + rifampin + pyrazinamide + ethambutol x 2 mo (initiation phase), then INH + rifampin x 4 mo in fully susceptible TB (continuation phase), total 6 mo. Extend continuation phase to 7 mo if >65, pregnant or risk of hepatotoxicity
- extrapulmonary TB: same regimen as pulmonary TB but increase to 12 mo in bone/joint, CNS, and miliary/disseminated TB + corticosteroids for meningitis, pericarditis
- empiric treatment of suspected MDR (multidrug resistant) or XDR (extensively drug-resistant) TB requires referral to a specialist
  - MDR = resistance to INH and rifampin ± others
  - XDR = resistance to INH + rifampin + fluoroquinolone + ≥1 of injectable, second-line agents
- very difficult to treat, global public health threat, 5 documented cases in Canada from 1997-2008
  - suspect MDR TB if previous treatment, exposure to known MDR index case, or immigration from a high-risk area
- note: TB is a reportable disease to Public Health (please see Public Health Agency of Canada website for more information)

**Positive TST Test**
If induration at 48-72 h
>5 mm if immunocompromised, close contact with active TB
>10 mm all others; positive PPD CXR; decision to treat depends on individual risk factors
**False(–):** poor technique, anergy, immunosuppression, infection <10 wk or remotely
**False(+):** BCG after 12 mo of age in a low-risk individual, NTM
Booster effect: initially false(–) result boost to a true(+) result by the testing procedure itself (usually if patient was infected long ago so had diminished delayed type hypersensitivity reaction or if history of BCG)

**TB Treatment**

**RIPE**
**R**ifampin, **I**NH, **P**yrazinamide, **E**thambutol

# HIV and AIDS

## Epidemiology

### Canadian Situation (Public Health Agency of Canada, 2016)

- estimated 65,040 Canadians living with HIV infection at the end of 2016, 20% unaware of HIV-positive status
- 2090 new infections were reported in 2013: MSM account for 53% of cases, IDU 19%

### Global Situation (WHO and UNAIDS Core Epidemiology Slides, July 2018)

- estimated 36.7 million people living with HIV/AIDS at the end of 2016
- estimated 1.8 million newly infected in 2016
- estimated 1 million AIDS-related deaths in 2016

## Etiology

- HIV is a retrovirus that causes progressive immune system dysfunction, predisposing patients to various opportunistic infections and malignancies
- HIV virion includes an envelope (gp41 and gp120 glycoproteins), matrix (p17) and capsid (p24), enclosing 2 single-stranded copies of RNA plus enzymes in its core
- virion glycoproteins bind CD4 and CCR5/CXCR4 on CD4+ T lymphocytes (T-helper cells) to fuse and enter the cells
- RNA converted to dsDNA by viral reverse transcriptase; dsDNA is integrated into host genome by viral integrase
- virus DNA transcribed and translated using host cell machinery, post-translational modifications include proteolytic activity of virally encoded protease enzymes
- newly produced virions bud out of host cell, incorporating host cell membrane; additional maturation steps are required before virion is considered infectious
- exact mechanisms of CD4 depletion incompletely characterized but likely include direct viral cytopathic effects, apoptosis, and increased cell turnover

# Modes of Transmission

**Table 18. Modes of Transmission in Adolescents and Adults by Site and Medium**

| HIV Invasion Site | Sub-Location | Transmission Medium | Transmission Probability per Exposure Event |
|---|---|---|---|
| Female genital tract | Vagina, ectocervix, endocervix | Semen | 1 in 200 to 1 in 2000 |
| Male genital tract | Inner foreskin, penile urethra | Cervicovaginal and rectal secretions and desquamations | 1 in 700 to 1 in 3000 |
| Intestinal tract | Rectum, upper GI tract | Semen<br>Semen<br>Maternal blood/genital secretions (intrapartum)<br>Breastmilk | 1 in 20 to 1 in 300<br>1 in 2500<br>1 in 5 to 1 in 10<br>1 in 5 to 1 in 10 |
| Placenta | Chorionic villi | Maternal blood (intrauterine) | 1 in 10 to 1 in 20 |
| Blood stream | | Contaminated blood products<br>Sharp/needlestick injuries | 95 in 100<br>1 in 150 |

Adapted with permission from Macmillan Publishers Ltd. Nat Rev Immunology 2008;8:447-457
NOTE: these estimates are for "all comers" i.e. they estimate transmission risk for anyone with HIV infection and do not take into account treatment status of the HIV+ person (in contrast to results of PARTNER study)

p24 = capsid protein
gp41 = fusion and entry
gp120 = attachment to host T-cell

Homozygosity for A32 mutation in CCR5 gene confers relative resistance to HIV infection
Heterozygosity for A32 mutation in CCR5 gene associated with slower disease course

# Natural History

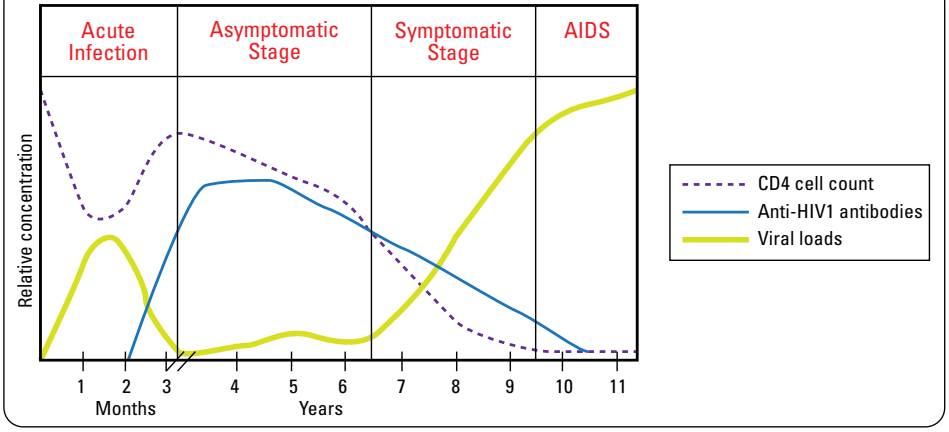



**Figure 7. Relationships between CD4 T-cell count, viral load, and anti-HIV antibodies**

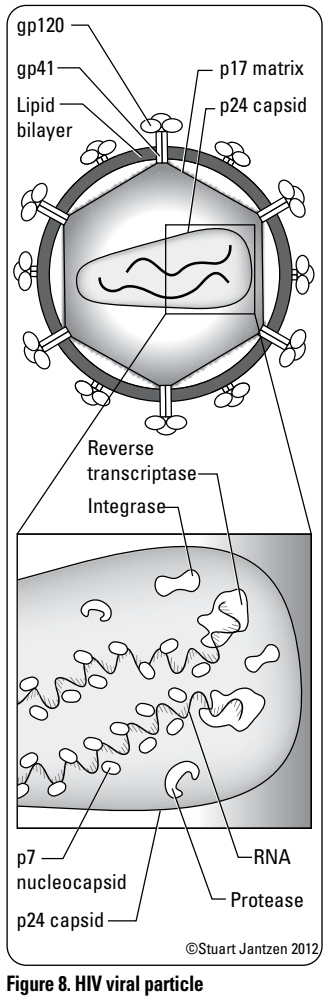



**Figure 8. HIV viral particle**

## Acute (Infection) Retroviral Syndrome

- 40-90% experience an acute "flu-like" illness (may include fever, pharyngitis, lymphadenopathy, rash, arthralgias, myalgias, headache, GI symptoms, oral ulcers, weight loss) 2-6 wk post-exposure lasting 10-15 d
- hematologic disturbances (lymphopenia, thrombocytopenia)
- 10-20% present with aseptic meningitis; HIV RNA and/or p24 may be detected in CSF
- associated with a high level of plasma viremia and therefore high risk of transmission

## Asymptomatic (Latent) Stage

- during latent phase, HIV infects and replicates in CD4+ T lymphocytes (lymph nodes)
- normal CD4 count in adults: 500-1100 cells/mm$^3$
- CD4 count drops 60-100 cells/mm$^3$ per year but is variable
- by 10 yr post-infection, 50% have advanced HIV (i.e. AIDS), 30% demonstrate milder symptoms, and <20% are asymptomatic if untreated

## Definition of AIDS

- HIV-positive AND one or more of the clinical illnesses that characterize AIDS, including: opportunistic infections (e.g. *Pneumocystis jiroveci* pneumonia (PJP, previously PCP), esophageal candidiasis, CMV, MAC, TB, toxoplasmosis), malignancy (Kaposi's sarcoma, invasive cervical cancer), wasting syndrome OR CD4 <200 (or <15%); this is largely historical since ART can reverse CD4 count decline

**Table 19. Symptomatic Stage (CD4 count thresholds for classic clinical manifestations)**

| CD4 Counts | Possible Manifestations |
|---|---|
| **<500 cells/mm³** | Often asymptomatic<br>Constitutional symptoms: fever, night sweats, fatigue, weight loss<br>Mucocutaneous lesions: seborrheic dermatitis, HSV, VZV (shingles), oral hairy leukoplakia (EBV), candidiasis (oral, esophageal, vaginal), Kaposi's sarcoma (KS)<br>Recurrent bacterial infections, especially pneumonia<br>Pulmonary and extrapulmonary tuberculosis<br>Lymphoma |
| **<200 cells/mm³** | *Pneumocystis jiroveci* pneumonia (formerly PCP)<br>KS<br>Oral thrush<br>Local and/or disseminated fungal infections: *Cryptococcus neoformans, Coccidioides immitis, Histoplasma capsulatum* |
| **<100 cells/mm³** | Progressive multifocal leukoencephalopathy (PML) – JC virus<br>CNS toxoplasmosis |
| **<50 cells/mm³** | CMV infection: retinitis, colitis, cholangiopathy, CNS disease<br>*Mycobacterium avium* complex (MAC)<br>*Bacillary angiomatosis* (disseminated *Bartonella*)<br>Primary central nervous system lymphoma (PCNSL) |

## Laboratory Diagnosis

- anti-HIV antibodies detectable after a median of 3 wk, virtually all by 3 mo (therefore 3 mo window period)
- initial screening test (3rd generation antibody test): enzyme linked immunosorbent assay (ELISA) detects serum antibody to HIV; sensitivity >99.5%
- increasingly, combination p24 antigen/HIV antibody tests (4th generation) used for screening; improved sensitivity in early or acute infection and sensitivity/specificity approach 100% for chronic infection
- confirmatory test: if positive screen, Western blot confirmation by detection of antibodies to at least two different HIV protein bands (p24, gp41, gp120/160); specificity >99.99%
- rapid (point of care) antibody tests: higher false positives, therefore need to confirm positive results with traditional serology
- p24 antigen: detection by ELISA may be positive during "window period"

## Management of the HIV-Positive Patient

- verify positive HIV test
- complete baseline history and physical exam, then follow-up every 3-6 mo
- laboratory evaluation
  - if non-stable and non-suppressed viral load, order routine CD4 count to measure status of the immune system
  - routine HIV-RNA levels (viral load) also important indicator of effect of ART
  - baseline HIV resistance testing to guide ARV therapy
  - HLA-B*5701 genetic test to screen for abacavir hypersensitivity if considering abacavir in treatment regimen
  - CCR5 tropism testing if considering CCR5 antagonist in treatment regimen
  - baseline tuberculin skin test (PPD): induration greater than 5 mm is positive
  - baseline serologies (hepatitis A, B, and C, syphilis, toxoplasmosis, CMV, VZV)
  - routine biochemistry and hematology, CXR, urinalysis
  - annual fasting lipid profile and fasting glucose (due to ART side effects)
- education
  - regular follow-up on CD4 counts and viral loads (q3-6mo) (not necessary if suppressed viral load) as well as strict adherence to ART improves prognosis
  - prevention of further transmission through safer sex and clean needles for IDU
  - HIV superinfection (transmission of different HIV strains from another HIV+ person) does rarely occur so barrier protection during sex is still recommended
  - discuss importance of disclosing HIV status to partners including risk of criminal prosecution of non-disclosure in jurisdictions where applicable
  - connect to relevant community groups and resources
- health care maintenance
  - assessment of psychosocial concerns and referral to psychiatry or social work if appropriate
  - vaccines: influenza annually, 23-valent pneumococcal every 5 yr, HBV (if not immune), HAV (if seronegative), HPV
  - annual screening (PAP smear, STIs)
  - management of comorbid conditions and provision of general primary care



**Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy**
JAMA 2016;316(2):171-81
**Objective**: To evaluate the rate of within-couple HIV transmission (heterosexual and MSM) during periods of sex without condoms and when the HIV+ partner had HIV-1 RNA <200 copies/mL.
**Methods**: Prospective, observational PARTNER study, enrolled 1166 HIV serodifferent couples (in which the HIV+ partner was taking ART) reported having condomless sex. Primary outcome was risk of within-couple HIV transmission to HIV- partner.
**Results**: Enrolled couples provided 1238 eligible couple-years of follow-up. Couples reported condomless sex for a median of 2 yr and condomless sex with other partners was reported by 108 HIV- MSM and 21 heterosexuals. While 11 HIV- partners became HIV+ (10 MSM; 1 heterosexual), no phylogenetically linked transmissions occurred over eligible couple-years of follow-up (within-couple HIV transmission = 0, 95% CI 0.30-0.71 per 100 couple-years).
**Conclusions**: Among serodifferent heterosexual and MSM couples in which HIV+ partner was using ART and who reported condomless sex, during median 1.3 yr/couple follow-up, there were no documented cases of within-couple transmission.



**Seroconversion:** Development of detectable anti-HIV antibodies

**Window Period:** Time between infection and development of anti-HIV antibodies; when serologic tests (ELISA, Western blot) are negative



All infants born to HIV infected mothers have positive ELISA tests because of circulating maternal anti-HIV antibodies, which disappear by 18 mo; early diagnosis is made by detection of HIV RNA in plasma



**HLA-B*5701 Testing**
Abacavir hypersensitivity reactions usually only occur in individuals carrying this HLA allele (~5-7% of Caucasians, lower prevalence in other ethnic groups). Routine screening for HLA-B*5701 at baseline and definitely prior to abacavir use



**HIV Status**
- CD4 count: progress and stage of disease
- Viral load: rate of progression

**Table 20. Prophylaxis Against Opportunistic Infections in HIV-infected Patients**

| Pathogen | Indication for Prophylaxis | Prophylactic Regimen |
|---|---|---|
| *Pneumocystis jiroveci* | CD4 count <200 cells/mm$^3$ or history of oral candidiasis | TMP-SMX 1 SS or DS OD |
| *Toxoplasma gondii* | IgG antibody to *Toxoplasma* and CD4 count <100 cells/mm$^3$ | TMP-SMX 1 DS OD |
| *Mycobacterium tuberculosis* | PPD reaction >5 mm or contact with case of active TB | INH + pyridoxine daily x 9 mo<br>Rifampin daily x4mo<br>Rifapentine + INH + pyridoxine daily x 12 wk |
| *Mycobacterium avium* complex | CD4 count <50 cells/mm$^3$ | No prophylaxis if patients are started ARTs |

SS = single strength; DS = double strength
See USPHS/IDSA guidelines for preventing opportunistic infections among HIV-infected persons (Relevant Sections updated 2013, 2015). Available from: http://aidsinfo.nih.gov/

# Anti-Retroviral Treatment

## Overall Treatment Principles

- recommended that all HIV+ patients initiate combination ART to restore and preserve immune function, reduce morbidity, prolong survival, and prevent transmission
- patients starting ART should be committed to treatment and understand the importance of adherence; poor compliance can lead to viral resistance; may defer treatment on the basis of clinical and psychosocial factors on case by case basis
- consider results of baseline resistance testing and complete ART history before (re-) initiating ART
- goal: keep viral load below limit of detection i.e. <40 copies/mL (undetectable); viral load should decrease 10-fold within 4-8 wk, be undetectable by 6 mo, and restore immunological function
- strong evidence against intermittent ART or 'drug holidays'
- patient with undetectable viral load adhering to ART does not transmit HIV to sexual partners

## ART Recommendations for Treatment of Naïve Patients

- 2 NRTIs + 1 INSTI/PI (boosted with ritonavir or cobicistat)
- **note**: guidelines are subject to frequent change. Combination therapy is suggested, preferably with single pill regimens

## Treatment Failure

- defined primarily by viral load (persistently >200 copies/mL)
- ensure that viral load >40 is not just a transient viremia or 'blip'; confirm medication adherence, assess drug interactions, perform resistance testing

**Table 21. Anti-Retroviral Drugs**

| Class | Drugs | Mechanism | Adverse Effects |
|---|---|---|---|
| **Nucleoside reverse transcriptase inhibitors (NRTIs)** | abacavir (ABC)<br>emtricitabine (FTC)<br>lamivudine (3TC)<br>tenofovir disoproxil fumarate (TDF)<br>zidovudine (AZT)<br>**Combination Tablets:**<br>AZT/3TC (Combivir®)<br>AZT/3TC/ABC (Trizivir®)<br>ABC/3TC (Kivexa®)<br>TDF/FTC (Truvada®) | Incorporated into the growing viral DNA chain, thereby competitively inhibiting reverse transcriptase and terminating viral DNA growth | Lactic acidosis (often secondary to mitochondrial toxicity)<br>Lipodystrophy<br>Rash<br>Nausea/vomiting/diarrhea<br>Bone marrow suppression (AZT)<br>Peripheral neuropathy (ddI, d4T)<br>Drug-induced hypersensitivity (ABC)<br>Pancreatitis (ddI/d4T)<br>Myopathy (AZT) |
| **Non-nucleoside reverse transcriptase inhibitors (NNRTIs)** | delavirdine (DLV)<br>doravirine (DOR)<br>efavirenz (EFZ)<br>etravirine (ETR)<br>nevirapine (NVP)<br>rilpivirine (RPV) | Non-competitively inhibit function of reverse transcriptase, thereby preventing viral RNA replication | Rash, Stevens-Johnson syndrome<br>CNS: dizziness, insomnia, somnolence, abnormal dreams (efavirenz)<br>Hepatotoxicity (nevirapine – avoid in females with CD4 >250, men with CD4 >400)<br>CYP3A4 interactions |
| **Protease inhibitors (PIs)*** | atazanavir (ATV)<br>darunavir (DRV)<br>lopinavir/ritonavir (LPV/r)<br>nelfinavir (NFV)<br>ritonavir (RTV)<br>*tipranavir* (TPV) | Prevent maturation of infectious virions by inhibiting the cleavage of polyproteins | Lipodystrophy, metabolic syndrome<br>Nausea/vomiting/diarrhea<br>Nephrolithiasis (indinavir)<br>Rash (APV)<br>Hyperbilirubinemia (atazanavir, indinavir)<br>CYP3A4 interactions<br>Hyperlipidemia |
| **Integrase strand transfer inhibitors (INSTIs)** | bictegravir<br>dolutegravir (DTG)<br>elvitegravir (EVG)<br>raltegravir (RAL) | Inhibits integration of HIV DNA into the human genome thus preventing HIV replication | |
| **Fusion inhibitor (only used if resistance)** | enfuvirtide (T-20) | Inhibit viral fusion with T-cells by inhibiting gp41, preventing cell infection | Injection site reactions, rash, infection, diarrhea, nausea, fatigue |
| **CCR5 antagonist** | maraviroc (MVC) | Inhibit viral entry by blocking host CCR5 co-receptor | Fever, cough, dizziness |

*Standard of care is to pharmacologically boost most PIs with ritonavir to increase concentrations

1° and 2° prophylaxis may be discontinued if CD4 count is above threshold for ≥6 mo while on ART

**Anti-Retroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals**
Cochrane DB Syst Rev 2012 Jul 11;7:CD007189
**Purpose**: To evaluate the efficacy of oral anti-retroviral prophylactic therapy in preventing HIV infection.
**Study**: Systematic review of 12 randomized controlled trials with 6 trials forming the core analysis.
**Population**: 9849 HIV-uninfected patients at high risk of contracting HIV including men who have sex with men, serodiscordant couples, and others.
**Outcome**: New infection with HIV.
**Results**: Daily oral tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) reduced the risk of HIV acquisition compared to placebo (RR 0.49; 95% CI 0.28-0.85). TDF alone also showed significant risk reduction in trials with fewer patients (RR 0.33; 95% CI 0.20-0.55). There was no significant increase in adverse events in any of the treatment groups. Sexual practices and adherence did not differ between treatment and placebo arms.
**Conclusions**: Pre-exposure prophylaxis with TDF with or without FTC effectively reduces the risk of HIV aquisition in high risk, HIV uninfected patients without causing significant adverse effects.

**Reasons for Deterioration of a Patient with HIV/AIDS**

- Opportunistic infections
- Neoplasms
- Medication-related toxicities
- Co-infections (e.g. HBV, HCV, STIs)
- Non-AIDS-related comorbidities (e.g. cardiovascular, renal, hepatic, neurocognitive, bone disease)

**Treatment Failure**

- Assess adherence
- Assess drug interactions
- Resistance testing
- Rule out opportunistic infections
- Rule out marrow suppression
- Construct new 3-drug regimen

**Lactic Acidosis**

- Occurs secondary to mitochondrial toxicity
- Symptoms include abdominal pain, fatigue, nausea/vomiting, muscle weakness

**Lipodystrophy**
Body fat redistribution (mainly with old ARVs)

- Lipohypertrophy (e.g. dorsal fat pad, breast enlargement, increased abdominal girth) thought to be caused primarily by protease inhibitors
- Lipoatrophy (e.g. facial thinning, decreased adipose tissue in the extremities) is thought to be caused by thymidine analogue NRTIs such as d4T and AZT
- Metabolic abnormalities: lipids (increased LDL, increased TGs), glucose (insulin resistance, type 2 DM), increased risk of CVD

## Single Tablet ART Regimens

- reduces pill burden and increases adherence
- generally better tolerated

**Table 22. Single Tablet ART Regimens**

| Name | Contents | Common Side Effects |
|---|---|---|
| **Genvoya®** | tenofovir/emtricitabine/elvitegravir/cobicistat | good side effect profile |
| **Complera®** | rilpivirine/emtricitabine/tenofovir | good side effect profile |
| **Odefsey®** | rilpivirine/emtricitabine/tenofovir alafenamide | good side effect profile |
| **Stribild®** | elvitegravir/cobicistat/emtricitabine/tenofovir | good side effect profile |
| **Triumeq®** | dolutegravir/abacavir/lamivudine | good side effect profile; use only in HLAB*5701 negative patients |
| **Atripla®** | efavirenz/tenofovir/emtricitabine | psychiatric events, vivid dreams |

*Standard of care is to pharmacologically boost most PIs with ritonavir to increase concentrations

## Recommended ARV Regimens for Treatment-Naïve HIV-infected Adults

- initial regimens for treatment (all include an integrase inhibitor and a pair of NRTIs):
  1. Bictegravir/TAF/FTC
  2. Dolutegravir/ABC/3TC
  3. Dolutegravir + TAF (or TDF)/FTC
  4. Elvitegravir/cobicistat/TAF (or TDF)/FTC
  5. Raltegravir + TAF (or TDF)/FTC

  Note: Not all regimens available in all regions.

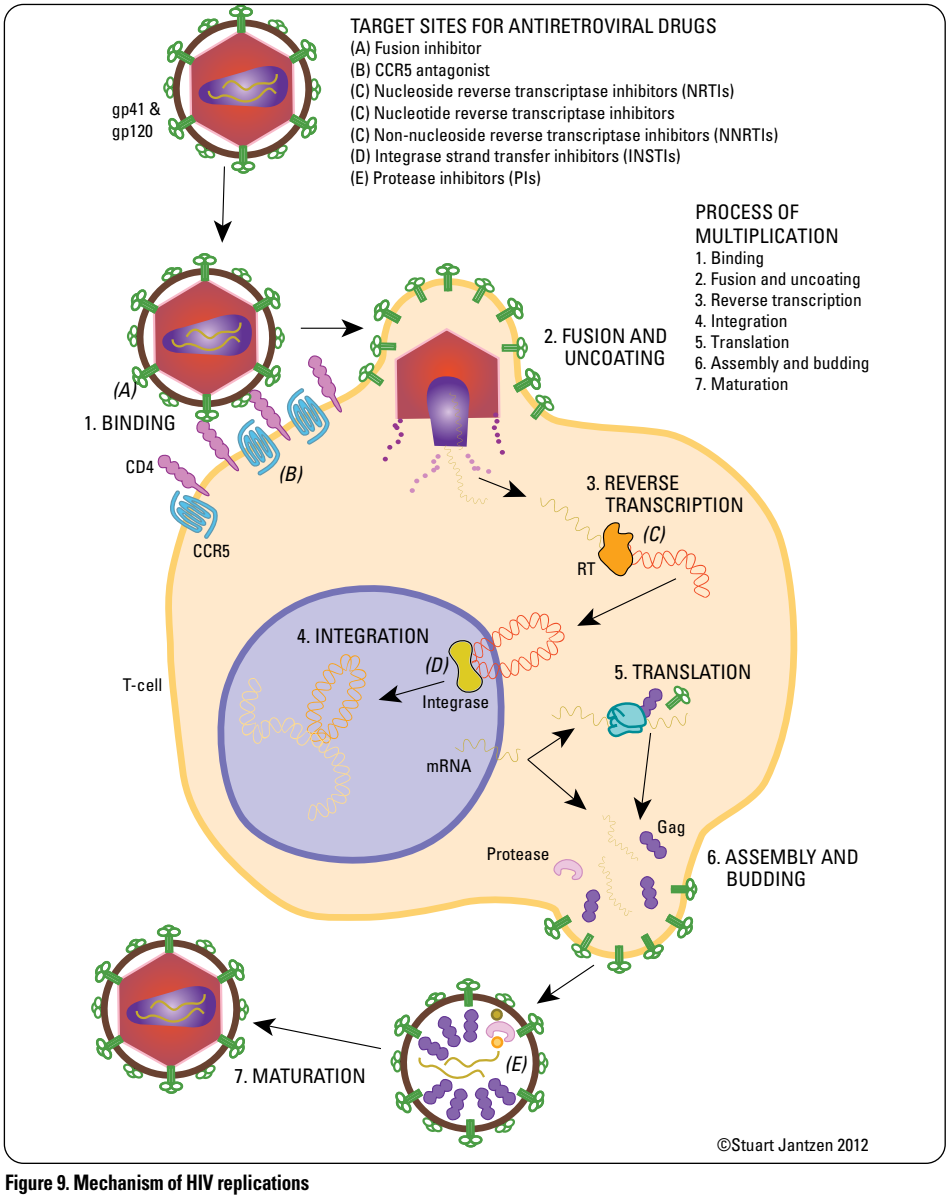



**Figure 9. Mechanism of HIV replications**

# Prevention of HIV Infection

- education, including harm-reduction
  - safer sexual practices: condoms for vaginal and anal sex, barriers for oral sex
  - harm reduction for IVDU: avoid sharing needles
- prevention of vertical HIV infection: treatment with ART should be initiated prior to pregnancy or as early as possible during pregnancy. The risk of vertical HIV transmission can be reduced to <1% if maternal ART is started in a timely manner and the maternal viral load is undetectable prior to delivery
- universal blood and body precautions for health care workers
  - post-exposure prophylaxis (PEP) after occupational (e.g. needle-stick injury) and non-occupational (e.g. consensual sex, sexual assault) exposure to HIV: 2- or 3-drug regimen initiated immediately (<72 h) after exposure and continuing for 4 wk
- recent data has demonstrated efficacy of pre-exposure prophylaxis (oral PrEP or topical microbicides) in preventing HIV
- ART associated with 96% reduction in risk of transmitting HIV to sexual partners
- screening of blood and organ donation

# Types of Testing

**1. Nominal/Name-Based HIV Testing**
- person ordering the test knows the identity of the person being tested for HIV
- HIV test is ordered using the name of the person being tested
- person ordering the test is legally obligated to notify Public Health officials if test results are positive for HIV
- test result is recorded in the health care record of the person being tested

**2. Non-Nominal/Non-Identifying HIV Testing**
- similar to nominal/name-based testing on all points except:
  - HIV test is ordered using a code or the initials of the person being tested

**3. Anonymous Testing**
- available at specialized clinics
- person ordering the HIV test does not know the identity of the person being tested
- HIV test is carried out using a unique non-identifying code that only the person being tested for HIV knows
- test results are not recorded on the health care record of the person being tested
- patient identification and notification of Public Health required to gain access to ART

# HIV Pre- and Post-Test Counselling

- a diagnosis of HIV can be overwhelming and is often associated with stigma and discrimination
- consider pre- and post-test counselling, regardless of the results
- goals include: assessing risk, making informed decision to be tested, education to protect themselves and others from virus exposure, where to go for more information and support
- HIV+ patients should be connected with local support services



Early identification of HIV is essential for patients to receive the maximal benefit from ART



**Efficacy, Safety, and Effect on Sexual Behaviour of On-Demand Pre-Exposure Prophylaxis for HIV in Men Who Have Sex With Men: An Observational Cohort Study**
Lancet HIV 2017;4(9):e402-10.
**Objective**: Assess the efficacy, safety, and effect of on-demand pre-exposure prophylaxis (PrEP) on sexual behaviour.
**Methods**: Men and transgender women who have sex with men, previously enrolled in the placebo-controlled ANRS IPERGAU trial. On demand tenofovir disoproxil fumarate (300 mg) and emtricitabine (200 mg) to be taken before and after sexual intercourse and participants assessed for incidence of HIV, PrEP adherence, safety, and sexual behaviour.
**Results**: HIV incidence was 0.19/100 person-years (95% CI 0.01-1.08) vs. 6.60/100 person-years (95% CI 3.60-11.05) in the placebo group, relative risk reduction of 97%. Drug-related GI events were reported in 14% of participants, but were self-limiting. Participants reporting condomless sex at their last receptive anal intercourse increased from 77 to 86% at 18 mo follow-up.
**Conclusions**: On-demand oral PrEP is highly effective at preventing HIV infection among high-risk men who have sex with men. This represents an alternative to daily PrEP.



**Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women**
NEJM 2016;375:2121-32.
**Objectives**: To evaluate whether longer-acting methods of anti-retroviral therapy (i.e. vaginal rings) may simplify use of medications and provide HIV-1 protection.
**Methods**: Phase 3, randomized, double-blind, placebo-controlled trial of monthly vaginal ring containing dapivirine in women (aged 18-45) in Malawi, South Africa, Uganda, and Zimbabwe.
**Results**: Among 2629 women enrolled, the incidence of HIV-1 infection was 3.3/100 person-years in dapivirine group and 4.5/100-years in placebo group. Post hoc analysis identified higher rates of HIV-1 protection in women >21 yr (56%, 95% CI 31-71) but not among those 21 yr (-27%, 95% CI -133-31), which correlated with reduced adherence.
**Conclusions**: Monthly vaginal ring containing dapivirine reduced risk of HIV-1 infection among African women.

# Fungal Infections

## Skin and Subcutaneous Infections

## Superficial Fungal Infections

- see Dermatology, D5

## Dermatophytes

- see Dermatology, D26

# Subcutaneous Fungal Infection

### Etiology
- subcutaneous inoculation by fungi that naturally reside in the soil, including *Sporothrix schenckii*, which usually occurs in gardeners injured by a rose thorn or splinter

### Clinical Feature
- causes subcutaneous nodules at the point of entry, may develop into an ulcer
- fungi may migrate up lymphatic vessels creating nodules along the way – "nodular lymphangitis"

### Treatment
- oral azole
- IV amphotericin B for severe or disseminated infection

# Endemic Mycoses



Histoplasmosis is commonly associated with exposure to chicken coops, bird roosts, and bat caves

### Etiology
- fungal infection that occurs through the inhalation of spores (from soil, bird droppings, vegetation) or inoculation injury
- thermally dimorphic organisms: mould in cold temperature (e.g. soil) and yeast at higher temperature (e.g. tissue)
- in North America, the three major endemic mycoses are: histoplasmosis, blastomycosis, and coccidioidmycosis

### Clinical Feature
- may be asymptomatic
- all can cause pneumonia and may disseminate hematogenously
- may reactivate or disseminate during immunocompromised states

### Treatment
- almost never empiric, and requires diagnosis first
- common to all endemic mycoses
  - oral azole (e.g. itraconazole for mild-moderate local infection)
  - IV amphotericin B for systemic infection

**Table 23. Endemic Mycoses**

| Disease | Endemic Region | Clinical Features | Investigations |
|---|---|---|---|
| ***Histoplasma capsulatum*** | Ohio and Mississippi River valleys in central USA, Ontario, Quebec; widespread | Asymptomatic (in most people)<br>Primary pulmonary<br>• Fever, cough, chest pain, headache, myalgia, anorexia<br>• CXR (acute): pulmonary infiltrates ± hilar lymphadenopathy<br>• CXR (chronic): pulmonary infiltrates, cavitary disease<br>Disseminated (rare)<br>• Occurs primarily in immunocompromised patients<br>• Spread to bone marrow (pancytopenia), GI tract (ulcers), lymph nodes (lymphadenitis), skin, liver, adrenals, CNS | Fungal culture, fungal stain<br>Antigen detection (urine and serum)<br>Serology |
| ***Blastomyces dermatitidis*** | States east of Mississippi River, Northern Ontario and along the Great Lakes | May be asymptomatic<br>Primary: acute or chronic pneumonia<br>• Fever, cough, chest pain, chills, night sweats, weight loss<br>• CXR (acute): lobar or segmental pneumonia<br>• CXR (chronic): lobar infiltrates, fibronodular interstitial disease<br>Disseminated<br>• Spread to skin (verrucous lesions that mimic skin cancer, ulcers, subcutaneous nodules), bones (osteomyelitis, osteolytic lesions), GU tract (prostatitis, epididymitis) | Sputum smear and culture<br>Direct examination of clinical specimens for characteristic broad-based budding yeast (sputum, tissue, purulent material) |
| ***Coccidioides immitis*** | Deserts in southwest USA, northwest Mexico | Primary<br>• "Valley fever": subacute fever, chills, cough, chest pain, sore throat, fatigue that lasts for wk to mo<br>• Can develop hypersensitivity with arthralgias, erythema nodosum<br>Disseminated<br>• Rare spread to skin (ulcers), joints (synovitis), bones (lytic lesions), meninges (meningitis)<br>• Common opportunistic infection in patients with HIV | Sputum culture<br>Direct examination of clinical specimens for characteristic yeast (sputum, tissue, purulent material) |

# Opportunistic Fungi

## *Pneumocystis jiroveci* (formerly *P. carinii*) Pneumonia: PJP or PCP

### Etiology
- respiratory exposure to unicellular fungi (previously classified as a protozoa)
- rarely transmitted from person to person
- without prophylaxis, HIV-positive patients with a CD4 count <200 cells/mm3 have an 80% lifetime risk of PJP

### Clinical Feature
- symptoms of pneumonia: fever, non-productive cough, progressive dyspnea (and hypoxia)
- classic CXR findings of interstitial pneumonia
- most clinical disease is due to reactivation of latent infection or reinfection by a different genotype in immunocompromised patients (steroid use, HIV)

**CXR in *P. jiroveci***
- Bilateral, diffuse opacities
- CXR may be normal (20-30% cases)
- CT shows cysts (hence the name Pneumo"cystis") but almost never pleural effusions

### Investigations
- serum LDH elevated in nearly all cases
- visualization (immunofluorescence) or detection (PCR) of organism in induced sputum, bronchoalveolar lavage, or endotracheal aspirate (if intubated)

### Treatment and Prevention
- oxygen to keep $SaO_2$ >90%
- antimicrobial options
  - TMP/SMX (PO or IV) is preferred therapy
  - dapsone and TMP
  - clindamycin and primaquine
  - pentamidine (IV) is second line in severe disease
  - atovaquone
- corticosteroids used as adjuvant therapy in those with severe hypoxia ($pO_2$ <70 mmHg or A-a gradient $O_2$ >35 mmHg)
- prophylactic TMP/SMX for those at high risk of infection (HIV patients when CD4 <200 cells/$mm^3$ or non-HIV immunocompromised patients under specific conditions)

## *Cryptococcus* spp.

### Etiology
- inhalation of airborne encapsulated yeast from soil contaminated with pigeon droppings (*C. neoformans*) or certain tree species such as Eucalyptus or Douglas fir (*C. gatti*)
- *C. neoformans* tends to affect immunocompromised hosts vs. *C. gatti* which tends to affect immunocompetent hosts

*C. gattii* sees limited geographical distribution including Vancouver Island, Northern Australia, and Papua New Guinea

### Clinical Feature
- asymptomatic
- pulmonary
  - usually asymptomatic or self-limited pneumonitis
  - only 2% of HIV+ patients present with pulmonary symptoms including productive cough, chest tightness, and fever
- disseminated
  - frequently disseminates in HIV+ population
  - CNS: meningitis (leading cause of meningitis in patients with HIV)
  - skin: umbilicated papules that resemble large lesions of *Molluscum contagiosum*
  - other: bone, lymph nodes, bone marrow, soft tissues, eyes, prostate

### Investigations
- serum cryptococcal antigen
- CSF for meningitis: India-ink stain or cryptococcal antigen test, culture to confirm
- lateral flow cryptococcal antigen assay from serum and cerebrospinal fluid
- lumbar puncture with measurement of opening pressure

India-ink sensitivity for *Cryptococcus* is only 50% (higher in HIV patients); now replaced by cryptococcal antigen test in most laboratories

### Treatment
- in patients with HIV who have cryptococcal meningitis or severe pulmonary disease:
  - amphotericin B (+ flucytosine) is used in the first 2 wk for induction therapy; limited duration due to side effects
  - switch to fluconazole for at least 8 wk as consolidation therapy, then continue at lower dose for prolonged maintenance

# *Candida albicans*

### Etiology
- overgrowth of *C. albicans* (normally found as part of the microbiome of the skin, mouth, vagina, and GI tract)
- risk factors for overgrowth:
  - immunocompromised state (DM, corticosteroids)
  - critically ill patients (broad-spectrum antibiotic use, central venous catheters, TPN)
  - obesity → maceration and moisture in intertriginous areas, pannus, under breasts

### Clinical Feature
- mucocutaneous
  - oral thrush, esophagitis (chest pain, odynophagia), vulvovaginitis (see Gynecology, GY26), balanitis, cutaneous (diaper rash, skin folds, folliculitis), chronic mucocutaneous
  - small satellite lesions beyond the margin of the rash
- invasive
  - candidemia, endophthalmitis, endocarditis, UTI (upper tract), hepatosplenic disease

### Treatment
- thrush: nystatin suspension or pastilles for mild disease, fluconazole for severe disease
- vulvovaginal candidiasis: topical agents (imidazole or nystatin), oral fluconazole for recurrent disease
- cutaneous infection: topical imidazole
- opportunistic infections in HIV, other systemic infections: fluconazole or echinocandin
- chronic mucocutaneous: azoles

# *Aspergillus* spp.

### Etiology
- infection with *Aspergillus* fungi (*A. fumi, A. flavus*) which is found ubiquitously in the air and the environment
- *Aspergillus* produces a toxin called aflatoxin that contaminates nuts, grains, and rice

### Clinical Feature
- allergic bronchopulmonary aspergillosis (ABPA)
  - IgE-mediated asthma-type reaction with dyspnea, high fever, and transient pulmonary infiltrates
  - occurs more frequently in patients with asthma and allergies
- aspergilloma (fungus ball)
  - ball of hyphae in a pre-existing lung cavity
  - symptoms range from asymptomatic to massive hemoptysis
  - CXR: round opacity surrounded by a thin lucent rim of air, often in upper lobes ("air crescent" sign)
- invasive aspergillosis
  - associated with prolonged and persistent neutropenia or transplantation
  - pneumonia – most common
  - may disseminate to other organs: brain, skin
  - severe symptoms with fever, cough, dyspnea, cavitation; fatal if not treated early and aggressively
  - CXR: local or diffuse infiltrates ± pulmonary infarction, pulmonary nodules with surrounding ground glass ("halo" sign)
- mycotoxicosis
  - aflatoxin produced by *A. flavus* (nuts, grains, rice)
  - results in liver hemorrhage, necrosis, and hepatocellular carcinoma formation

### Treatment Options
- for invasive aspergillosis: voriconazole or amphotericin B
- surgical resection for aspergilloma
- corticosteroids ± itraconazole for Allergic Bronchopulmonary Aspergillosis

# Parasitic Infections

## Protozoa – Intestinal/Genitourinary Infections

### *Entamoeba histolytica* (Amoebiasis)

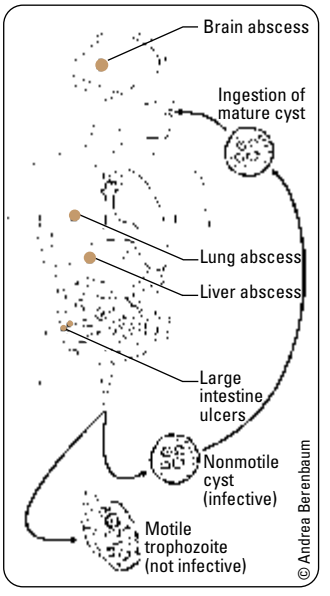



**Figure 10. *Entamoeba* life cycle**

#### Etiology
- infection with *E. histolytica* occurs when the cysts are transmitted via the oral-fecal route in areas of poor sanitation that have been contaminated by other infected humans
- seen in migrants, travellers, institutionalized individuals, Indigenous peoples, MSM

#### Clinical Feature
1. asymptomatic carriers
2. amoebic dysentery
   - abdominal pain, cramping, colitis, dysentery, low grade fever with bloody diarrhea secondary to local tissue destruction, and ulceration of large intestine
3. amoebic abscesses (liver abscesses, see General Surgery, GS48)
   - most common in liver (hematologic spread); presents with RUQ pain, weight loss, fever, hepatomegaly
   - can also occur in lungs and brain

#### Investigations
- serology, fecal/serum antigen testing, stool exam (for cysts and trophozoites), colon biopsy
- *E. histolytica* indistinguishable microscopically from the non-pathogen *E. dispar* (distinguish by specific stool antigen detection)

#### Treatment and Prevention
- metronidazole
- for invasive disease or cyst elimination: follow with iodoquinol or paromomycin
- aspiration of hepatic abscess if risk of cyst rupture, poor response to medical therapy, or diagnostic uncertainty
- asymptomatic cyst shedding: iodoquinol or paromomycin alone
- good personal hygiene, purification of water supply by boiling, filtration (not chlorination)

### *Giardia lamblia*

#### Etiology
- infection with *G. lamblia* occurs via the fecal-oral route with the ingestion of cysts from water/food contaminated by infected humans and other mammals (especially in the Rockies)
- risk factors: travel, camping, institutions, daycare centres, MSM

#### Clinical Feature
- giardiasis ("beaver fever")
  - symptoms vary from asymptomatic to self-limited mild watery diarrhea to malabsorption syndrome (chronic giardiasis where the parasite coats the small intestine and thus prevents fat absorption)
  - nausea, malaise, abdominal cramps, bloating, flatulence, fatigue, weight loss, steatorrhea
  - no hematochezia (no invasion into intestinal wall), no mucous in stool

#### Investigations
- multiple stool samples (daily x 3 d) for microscopy, stool antigen used occasionally
- occasionally small bowel aspirate or biopsy

#### Treatment and Prevention
- metronidazole; nitazoxanide if symptomatic
- good personal hygiene and sanitation, water purification (iodine better than chlorination), outbreak investigation

### *Trichomonas vaginalis*

#### Etiology
- infection with *T. vaginalis* occurs via sexual contact

#### Clinical Feature
- often asymptomatic (10-50%), especially males (occasionally urethritis, prostatitis)
- *Trichomonas* vaginitis (see Gynecology, GY26)
- vaginal discharge (profuse, malodourous, yellow-green or grey, frothy), pruritus, dysuria, dyspareunia

### Investigations
- wet mount (motile parasites), antigen detection, culture
- urine PCR to detect in males

### Treatment
- metronidazole for patient and partner(s)

*Trichomonas* causes 25% of vaginitis

## *Cryptosporidium* spp.

### Etiology
- infection with *Cryptosporidium* spp. via the fecal-oral route occurs with the ingestion of cysts from water contaminated by infected humans and other animals (including cows)
- risk factors: summer and fall, young children (daycare), MSM, contact with farm animals, immunodeficiency

### Clinical Feature
- range from self-limited watery diarrhea (immunocompetent) to chronic, severe, non-bloody diarrhea with nausea/vomiting, abdominal pain, and anorexia resulting in weight loss and death (immunocompromised)

### Investigations
- modified acid-fast stain of stool specimen, microscopic identification of oocysts in stool or tissue, stool antigen detection by direct fluorescent antibody

### Treatment and Prevention
- supportive care
- in HIV+ patients, (re)initiate ART and try to increase their CD4 count to >100; if fails, try nitazoxanide or macrolides
- good personal hygiene, water filtration

**Mefloquine for Preventing Malaria During Travel to Endemic Areas**
Cochrane DB Syst Rev 2017;CD006491.
**Objectives:** To summarize efficacy and safety of mefloquine used as prophylaxis for malaria in travellers.
**Methods:** RCTs (for efficacy and safety) and non-randomized cohort studies (for safety) to compare prophylactic mefloquine with placebo, no treatment, or alternative antimalarial agent.
**Results:** Participants were more likely to discontinue mefloquine (6%) vs. atovaquone-proguanil (3%) due to adverse effects (including nausea, vomiting, abnormal dreams, insomnia, anxiety, and depressed mood during travel). No difference in serious adverse effects or discontinuation due to adverse effects was found between mefloquine and doxycycline or mefloquine and chloroquine.
**Conclusions:** Absolute risk of malaria during short-term travel appears low with mefloquine, doxycycline, and atovaquone-proguanil therapy. Choice of agent depends on how individual travellers assess importance of specific adverse effects, pill burden, and cost.

# Blood and Tissue Infections

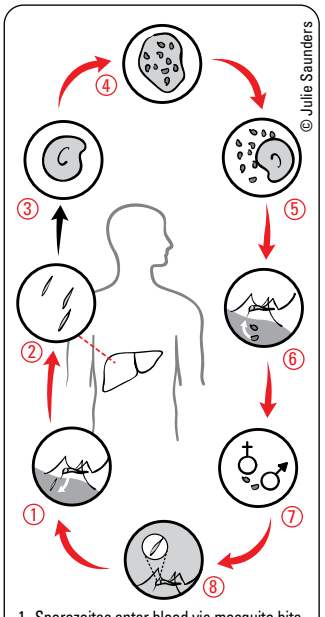
## *Plasmodium* spp. (Malaria)

### Etiology
- transmission of *Plasmodium* spp. (*P. falciparum, P. vivax, P. ovale, P. malariae, P. knowlesi*) primarily occurs during the blood meal of a night biting female Anopheles mosquito
- sporozoites injected during the blood meal then infect human liver cells, where they multiply and are released as merozoites; merozoites infect RBCs and cause disease
- infection with malaria parasites can also occur via vertical transmission (rare) or blood transfusion
- occurs in tropical/subtropical regions (sub-Saharan Africa, Oceania, South Asia, Central America, Southeast Asia, South America)

### Clinical Feature
- flu-like prodrome (may include fever, chills, fatigue, diaphoresis, cough, rash, arthralgias, myalgias, headache, GI symptoms)
- paroxysms of high spiking fever and shaking chills (due to synchronous systemic lysis of RBCs) (lasts several hours)
  - *P. vivax* and *P. ovale*: chills and fever x48 h but can be variable
  - *P. malariae*: chills and fever x72 h but can be variable
  - P. *falciparum*: less predictable fever interval, can be highly variable
- abdominal pain, diarrhea, myalgia, headache, and cough
- hepatosplenomegaly and thrombocytopenia without leukocytosis
- >90% of patients infected with *P. falciparum* are ill within 30 d
- relapsing malarial attacks may occur after many months due to the reactivation (entering the erythrocytic cycle) of dormant liver hypnozoites of either *P. ovale* or *P. vivax*
- complications:
  - *P. falciparum* (most common and most lethal): CNS involvement (cerebral malaria = seizures and coma), severe anemia, acute kidney injury, ARDS, primarily responsible for fatal disease
  - *P. knowlesi*, and rarely *P. vivax*, can be fatal

### Investigations
- CBC screen (assess for triad of: thrombocytopenia, elevated LDH, and atypical lymphocytes)
- microscopy: blood smear q12-24h (x3) to rule out infection
  - thick smear (Giemsa stain) for presence of organisms
  - thin smear (Giemsa stain) for species identification and quantification of parasites
- rapid antigen detection tests

Malaria is the most common fatal infectious disease worldwide




1. Sporozoites enter blood via mosquito bite, infect liver
2. Hepatic infiltration
3. Infect red blood cells
4. Trophozoite divides asexually many times to produce schizont (contains merozoites)
5. Red blood cell lyses and merozoites attack other red blood cells (chills and fever)
6. Male and female gametocytes (from merozoites) ingested by mosquito during bite
7. Male and female gametocytes (from merozoites) fuse in mosquito gut; produce ookinete
8. Ookinete matures into an oocyst which contains individual sporozoites; migrates to mosquito salivary glands

**Figure 11. Life cycle of *Plasmodium* spp.**

### Treatment and Prevention
- *P. vivax, P. ovale*: chloroquine (and primaquine to eradicate liver forms)
- *P. vivax*, chloroquine resistant: atovaquone/proguanil + primaquine or quinine and doxycycline + primaquine
- *P. malariae, P. knowlesi*: chloroquine
- *P. falciparum*: most areas of the world show chloroquine resistance – check local resistance patterns
  - artemisinin combination therapy (e.g. artesunate + doxycycline or clindamycin or atovaquone/proguanil)
  - atovaquone/proguanil combination (Malarone®)
  - quinine + doxycycline or clindamycin
  - mefloquine and artemisinin resistance increasing in southeast Asia (check local resistance)
- prevention with antimalarial prophylaxis (although quality may vary regionally), covering exposed skin, bed nets, insect repellent
- prevention of relapse for *P. vivax*: tafenoquine (in patients aged 16 years and older who are receiving appropriate antimalarial therapy for acute *P. vivax* infection)

**Drugs for Preventing Malaria in Travellers**
Cochrane DB Syst Rev 2009;CD006491
**Study**: Cochrane Systematic Review. 8 RCTs.
**Population**: 4240 non-immune adults and children traveling to regions with *P. falciparum* resistance to chloroquine.
**Intervention**: Atovaquone-proguanil, doxycycline, mefloquine, chloroquine-proguanil, or primaquine used for malaria prophylaxsis.
**Outcome**: Efficacy, safety, and tolerability.
**Results**: Atovaquone-proguanil and doxycycline had similar adverse events. Atovaquone-proguanil had fewer overall (RR 0.72), GI (RR 0.54), and neuropsychiatric events (RR 0.49) than mefloquine. Doxycycline also had fewer neuropsychiatric events than mefloquine (RR 0.84).
**Conclusion**: Atovaquone-proguanil or doxycycline as prophylaxis against malaria is best tolerated in terms of adverse effects and mefloquine is associated with adverse neuropsychiatric outcomes.

## *Trypanosoma cruzi*

### Etiology
- found in Mexico, South America, and Central America
- transmission by Reduviid insect vector ("Kissing Bug"), which defecates on skin and trypomastigotes in the stool are rubbed into bite site by host
- also transmitted via placental transfer, organ donation, blood transfusion, and ingestion of contaminated food containing Reduviid insects (especially cane juice)

### Clinical Feature
- American trypanosomiasis (Chagas disease)
  - acute: usually asymptomatic, local swelling at site of inoculation ("Romana's sign"; usually around one eye) with variable fever, lymphadenopathy, cardiomegaly, and hepatosplenomegaly
  - chronic indeterminate phase: asymptomatic but increasing levels of antibody in blood; most infected persons (60-70%) remain in this phase, and do not go on to manifest a determinate form of Chagas disease
  - chronic determinate: leads to chronic dilated cardiomyopathy, esophagomegaly, and megacolon 10-25 yr after acute infection in 30-40% of infected individuals

### Investigations
- wet prep and Giemsa stain of thick and thin blood smear, serology, PCR

### Treatment and Prevention
- acute: nifurtimox or benznidazole
- indeterminate: increasing trend to treat as acute infection for children and adults under age 50 years
- chronic determinate: symptomatic therapy, surgery as necessary including heart transplant, esophagectomy, and colectomy; there may be a benefit to antiparasitic treatment
- insect control, bed nets

**Classic Triad of Congenital Toxoplasmosis**
- Chorioretinitis
- Hydrocephalus
- Intracranial calcifications

## *Toxoplasma gondii*

### Etiology
- infection with *T. gondii* occurs through exposure to cat feces (oocysts), ingestion of undercooked meat (tissue cysts), vertical transmission, organ transplantation, gardening without gloves (cat oocyst exposure), whole blood transfusions, contaminated water sources

### Clinical Feature
- congenital
  - result of acute primary infection of mother during pregnancy (TORCH infection)
  - stillbirth (rare), chorioretinitis, blindness, seizures, severe developmental delay, microcephaly
  - initially asymptomatic infant may develop reactivation of chorioretinitis as adolescent or adult blurred vision, scotoma, ocular pain, photophobia, epiphora, hearing loss, developmental delay
- acquired
  - usually asymptomatic or mononucleosis-like syndrome in immunocompetent patient
  - infection remains latent for life unless reactivation due to immunosuppression
- immunocompromised (most commonly AIDS with CD4 <200)
  - encephalitis with focal CNS lesions seen as single or multiple ring-enhancing masses on CT (headache and focal neurological signs)
  - lymph node, liver, spleen enlargement, and pneumonitis
  - chorioretinitis

### Investigations
- serology, CSF Wright-Giemsa stain, antigen or DNA detection (PCR); pathology provides definitive diagnosis
- immunocompromised patients: consider CT scan (ring-enhancing lesion in cortex or deep nuclei) and ophthalmologic examination

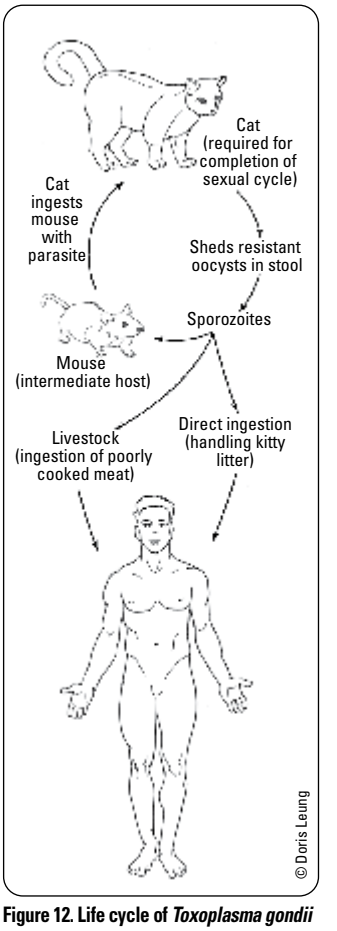



**Figure 12. Life cycle of *Toxoplasma gondii***

### Treatment and Prevention

- no treatment if: immunocompetent, not pregnant, no severe organ damage
- pregnancy: spiramycin to prevent transplacental transmission or pyrimethamine + sulfadiazine (add folinic acid), avoid undercooked meat and refrain from emptying cat litter boxes
- HIV: TMP/SMX
- proper hand hygiene, cook meat thoroughly to proper temperature

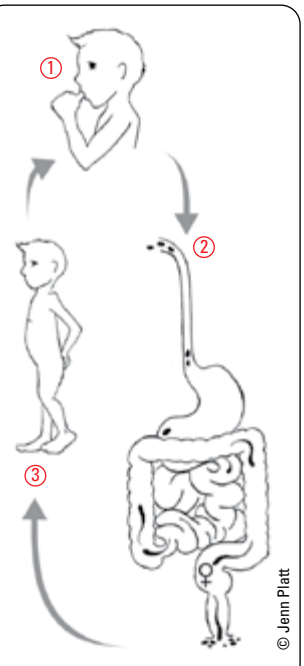
1/3 of Ontario's population is infected with *Toxoplasma gondii*

# Helminths

## Roundworms – Nematodes

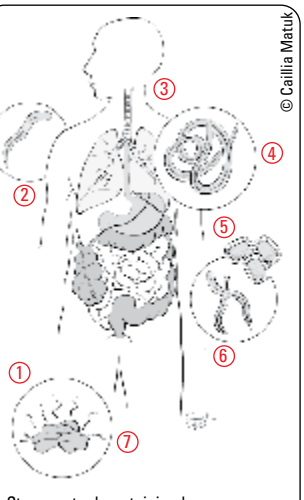
**Table 24. Nematodes (Roundworms)**

| Nematode | Epidemiology | Transmission | Medical Importance | Treatment |
|---|---|---|---|---|
| *Ascaris lumbricoides* | Tropics | Human feces, ingestion of contaminated food or water containing eggs | Abdominal pain and intestinal obstruction from high worm burden<br>Cough, dyspnea, pulmonary infiltrates from larval migration through lungs (Löffler's syndrome) | Mebendazole OR albendazole OR pyrantel pamoate |
| *Trichuris trichiura* (whipworm) | Tropics | Ingestion of eggs in soil | Diarrhea (± mucous, blood), abdominal pain, rectal prolapse, stunted growth | Mebendazole OR albendazole |
| *Onchocerca volvulus* | Africa, Latin America | Blackfly bite | River blindness (onchocerciasis), dermatitis | Ivermectin + doxycycline |
| *Wuchereria bancrofti* | Tropics | Mosquito bite | Damage to lymphatics resulting in lymphadenopathy, lymphedema, and elephantiasis Tropical pulmonary eosinophilia | Diethylcarbamazine + doxycycline |
| *Loa Loa* | Central Africa | Deer fly bite | Subcutaneous migration of worm, hyperresponsiveness in travellers | Diethylcarbamazine |
| *Enterobius vermicularis* (Pinworm) | Worldwide | Human host: fecal-oral self-inoculation and fomite person-to-person transfer<br>Adult worms live in cecum and deposit eggs in peri-anal skin | Asymptomatic carriers or severe nocturnal peri-anal itching (pruritus ani) Occasional vaginitis, ectopic migration to appendix or other pelvic organs Abdominal pain, nausea/vomiting with high worm burden | Sticky tape test: eggs adhere to tape applied to perianal skin (need 5-7 tests to rule out)<br>Examination of perianal skin at night may reveal adult worms<br>Usually no eosinophilia as no tissue invasion<br>Mebendazole, albendazole; pyrantel in pregnancy<br>Change underwear, bathe in morning, pajamas to bed, wash hands, trim fingernails<br>Treat all family members simultaneously<br>Reinfection common |
| *Strongyloides stercoralis* (Threadworm) | Subtropical, tropical, and temperate (including southern US) | Fecal contamination of soil: transmission via unbroken skin, walking barefoot<br>Autoinfection: penetration of larvae through GI mucosa or perianal skin<br>Adult worms live in mucosa of small intestine | One of few worms able to multiply in human host<br>Mostly asymptomatic infection or can have pruritic dermatitis at site of larval penetration<br>Transient pulmonary symptoms during pulmonary migration of larvae (eosinophilic pneumonitis = Löffler's syndrome)<br>Abdominal pain, diarrhea, pruritis ani, larva currens (itchy rash)<br>Hyperinfection: occasional fatal cases caused by massive auto-infection in immunocompromised host; immunoablative therapy, including high-dose corticosteroids, is the most common risk factor for disseminated infection | Ivermectin (OR Albendazole) |




1. Embryonated eggs ingested by humans
2. Larvae hatch in small intestine
3. Females migrate out anus at night

**Figure 13. Life cycle of *Enterobius***




1. Step on stool containing larvae
2. Larvae migrate to lungs via bloodstream
3. Larvae crawl up trachea and down to GI tract (cough/swallow)
4. Adult worms in intestine
5. Eggs produced in bowel
6. Larvae
7. Bowel movement containing larvae

**Figure 14. Life cycle of *Strongyloides***

# Flatworms

## Cestodes/Trematodes

**Table 25. Cestodes/Trematodes (Flatworms)**

| | Epidemiology | Transmission | Medical Importance | Treatment |
|---|---|---|---|---|
| **CESTODES** | | | | |
| *Taenia solium* | Developing countries | Undercooked pork (larvae), human feces (eggs) | Taeniasis: mild abdominal symptoms<br>Cysticercosis: mass lesions in CNS, eyes, skin, seizures | Corticosteroids + albendazole for cysticercosis<br>Antiepileptics if seizures<br>Praziquantel for adult tapeworm in gut (taeniasis) |
| *Taenia saginata* | Developing countries | Undercooked beef (larvae) | Mild GI symptoms | Praziquantel |
| *Diphyllobothrium latum* | Europe, North America, Asia | Raw fish | B12 deficiency leading to macrocytic anemia and posterior column deficits | Praziquantel |
| *Echinococcus granulosus* | Rural areas, Sheep-raising countries | Dog feces (eggs) | Liver/lung cysts (enlarge between 1-20 yr; may cause mass effect or rupture)<br>Risk of anaphylaxis if cystic fluid released during surgical evacuation | Albendazole ± praziquantel alone<br>Surgery + perioperative albendazole<br>Percutaneous aspiration + perioperative albendazole |
| **TREMATODES** | | | | |
| *Clonorchis sinensis* | Japan, Taiwan, China, SE Asia | Raw fish | Exists in bile ducts, causes inflammation and sometimes cholangiocarcinoma | Praziquantel |
| *Schistosoma* spp. | Africa, SE Asia, focal in Western Hemisphere | Fresh water exposure | Chronic sequelae secondary to long-term infection (e.g. chronic liver disease, SCC of the bladder) | Praziquantel |

## *Schistosoma* spp.

### Etiology

- infection with *Schistosoma* spp. (*S. mansoni, S. hematobium, S. japonicum*) occurs following penetration of unbroken skin by their larvae (cercariae) which are found in infested fresh water
- adult worms live in terminal venules of bladder/bowel passing eggs into urine/stool
- eggs must reach fresh water to hatch where they infect an intermediate host (snails) which then release cercariae into the water
- schistosomes cannot multiply in or pass between humans
- more common in individuals from sub-Saharan Africa, South America, Asia, Caribbean, Eastern Mediterranean/North Africa

### Clinical Feature

- most asymptomatic; symptoms seen in travellers (nonimmune)
- swimmer's itch: pruritic skin rash at site of penetration (cercarial dermatitis)
- acute schistosomiasis (Katayama fever): hypersensitivity to migrating parasites (4-8 wk after infection)
  - fever, hives, headache, weight loss, cough, abdominal pain, chronic diarrhea, high-grade eosinophilia
- chronic schistosomiasis (can persist for years):
  - *S. mansoni, S. japonicum*
    - worms in mesenteric vein, eggs in portal tracts of liver and bowel
    - heavy infections: intestinal polyps, portal and pulmonary HTN, splenomegaly (2° to portal HTN), hepatomegaly
  - *S. hematobium*
    - worms in vesical plexus, eggs in distal ureter and bladder induce granulomas and fibrosis
    - hematuria and obstructive uropathy; associated with squamous cell bladder cancer
  - neurologic complications: spinal cord neuroschistosomiasis (transverse myelitis), cerebral or cerebellar neuroschistosomiasis (increased ICP, focal CNS signs, seizures)
  - pulmonary complications: granulomatous pulmonary endarteritis, pulmonary HTN, cor pulmonale; especially in patients with hepatosplenic involvement

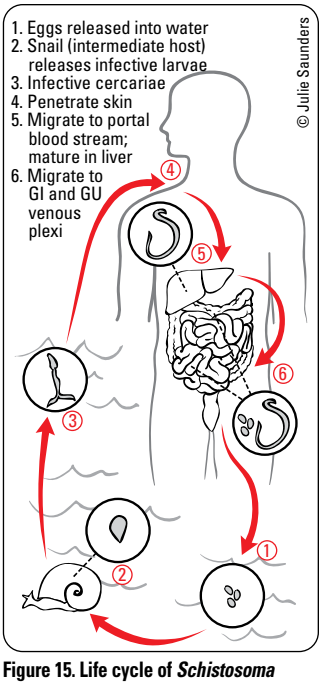



**Figure 15. Life cycle of *Schistosoma***

### Investigations

- serology (high sensitivity and specificity), CBC (eosinophilia, anemia, thrombocytopenia), loop-mediated isothermal amplification
- *S. mansoni, S. japonicum*: eggs in stool, liver U/S shows fibrosis, rectal biopsy
- *S. hematobium*: bladder biopsy, eggs in urine and occasionally stool, kidney and bladder U/S

### Treatment and Prevention
- praziquantel
- add glucocorticoid if acute schistosomiasis or neurologic complications develop
- proper disposal of human fecal waste, molluscicide (pesticide against molluscs), avoidance of infested fresh water while traveling

## Ectoparasites
- scabies, lice
- see Dermatology, D27

# Travel Medicine

## General Travel Precautions
- vector-borne: long sleeves, long pants, hats, repellents (containing permethrin) applied to clothes, belongings, and bed nets, and skin repellents (such as DEET) applied to exposed skin
- food/water: avoid eating raw meats/seafood, uncooked vegetables, and milk/dairy products; drink only bottled beverages, chlorinated water, boiled water
- recreation: caution when swimming in schistosomiasis-endemic regions (Lake Malawi), fresh water rafting/kayaking, beaches that may contain human/animal waste products, near storm drains, after heavy rainfalls
- prophylaxis: malaria (chloroquine, mefloquine, atovaquone + proguanil, doxycycline), traveller's diarrhea (bismuth salicylate)
- standard vaccines up to date (hepatitis B, MMR, tetanus/diphtheria, varicella, pertussis, polio, influenza)
- travel vaccines: hepatitis A/B, Japanese encephalitis, typhoid fever, yellow fever, rabies, ETEC, cholera
- sexually transmitted and blood-borne infections: safe sex practices, avoidance of percutaneous injury through razors, tattoos, piercings

### Infectious Diseases to Consider
- vector borne: malaria, dengue fever, Chikungunya, yellow fever, spotted fever rickettsioses, West Nile virus, trypanosomiasis, Japanese encephalitis, tick-borne encephalitis, leishmaniasis, Zika virus
- sexually transmitted: HIV, HBV, acute HSV, syphilis, usual STIs
- zoonotic: rabies, hantavirus, tularemia, Q fever, anthrax, brucellosis
- airborne: TB
- food/water: HAV, HEV, brucellosis, typhoid, paratyphoid, amoebiasis, dysentery, traveller's diarrhea, cholera, *Campylobacter* spp.
- soil/water: schistosomiasis, strongyloidiasis, leptospirosis, cutaneous larva migrans, histoplasmosis, paracoccidioidomycosis

## Fever in the Returned Traveller

### Etiology
- commonly identified causes of fever in returning traveller
  - parasitic: malaria (20-30%)
  - viral: non-specific mononucleosis-like syndrome (4-25%), dengue (5%), viral hepatitis (3%)
  - bacterial: typhoid from *Salmonella* (2-7%), rickettsioses (3%)
  - diverse group of causative pathogens: traveller's diarrhea (10-20%), RTI (10-15%), UTI/STI (2-3%)
- febrile illness in travellers can be caused by routine infections that are common in non-travellers (e.g. URTI, UTI)
- less commonly, fever can be due to non-infectious causes (e.g. DVT, PE)

### History
- pre-travel preparation
- travel itinerary: when, where, why, what, who, how?
  - dates of travel (determine incubation period)
  - season of travel: wet or dry
  - destination: country, region (urban or rural), environment (jungle, desert, etc.)
  - purpose of trip
- persons visiting friends and family more likely to be exposed to local population and pathogens
  - style of travel: lodgings, camping, adventure travelling
  - local population: sick contacts
  - transportation: use of animals



For up to date information on geographic and seasonal patterns of disease and travel advisories, check the website for the United States Centres for Disease Control and Prevention (wwwnc.cdc.gov/travel) or Foreign Affairs Canada (travel.gc.ca)



**Important Exposures**

| | |
|---|---|
| **Insect Bites** | |
| Mosquito | • *Plasmodium* spp. (Malaria)<br>• Dengue<br>• *Chikunguny*<br>• Lymphatic filariasis (Elephantiasis)<br>• West Nile Encephalitis<br>• Yellow Fever<br>• Japanese Encephalitis |
| Tick | • *Borrelia burgdorferi* (Lyme Disease)<br>• *Rickettsia rickettsii* (Rocky Mountain Spotted Fever) |
| Fly | • *Trypanosoma brucei* spp. (African sleeping sickness)<br>• *Leishmania* spp. (Leishmaniasis)<br>• *Bartonella bacilliformis* (Bartonellosis) |
| Flea | • *Yersinia* (Plague)<br>• *Tunga penetrans* (Tungiasis) |
| **Mammal Bites** | |
| Dog/Cat | • Rabies, *Pasteurella*, anaerobes, *Streptococcus, S. aureus* |
| Human | • *Streptococcus, S. aureus*, oral anaerobes, *Eikenella* |
| **Oral Exposures** | |
| Unpasteurized Milk | • *Brucella* spp., non-tuberculous *Mycobacteria, Salmonella, E. coli, Listeria* |
| Undercooked Meat/Fish | • Enteric bacteria, helminths, protozoa |
| Water | • Hepatitis A/E, Norwalk, cholera, *Salmonella, Shigella, Giardia,* poliovirus, *Cryptosporidium, Cyclospora* |
| **Environmental Exposures** | |
| Fresh Water | • *Leptospira* spp., schistosomes, *Acanthamoeba, Naegleria fowleri* |
| Soil | • Hookworms, *Toxocara* spp. (visceral larva migrans), *Leptospira interrogans* (leptospirosis) |

Adapted with permission from *Lancet* 2003;361:1459-69

- exposure history
  - street foods, untreated water: increased risk of traveller's diarrhea, enteric fever
  - uncooked meat/unpasteurized dairy: increased risk of parasitic infection
  - body fluids (sexual contacts, tattoos, piercings, IVDU, other injections)
  - increased risk of HBV, HCV, HIV, GC, *C. trachomatis*, syphilis
  - animal/insect bites: increased risk of malaria, dengue, rickettsioses, rabies
- fever pattern
- incubation period: use the earliest and latest possible dates of exposure to narrow the differential diagnosis and exclude serious infections
  - <21 d: consider malaria, typhoid fever, dengue fever, chikunguny, rickettsioses; exclude HBV, TB
  - >21 d: consider malaria, TB, typhoid fever; exclude dengue fever, chikungunya, traveller's diarrhea, rickettsioses
- body systems affected: GI, respiratory, CNS, skin

## Investigations

- all travellers with fever should undergo the following tests
  - blood work: CBC and differential, liver enzymes, electrolytes, creatinine, thick and thin blood smears x3 (for malaria), blood C&S
  - urine: urinalysis, urine C&S if dysuria or other localizing signs
- special tests based on symptoms, exposure history, and geography
  - stool: C&S, O&P
  - CXR
  - dengue serology for IgM



Fever in traveller from malaria endemic area is malaria until proven otherwise



**Pregnancy and Zika Virus**
For women and men who have been diagnosed with Zika virus or who have symptoms of Zika including fever, rash, joint pain or red eyes after possible exposure to Zika virus, CDC recommends:
- Women wait at least 8 wk after their symptoms first appeared before trying to get pregnant
- Men wait at least 6 mo after their symptoms first appeared to have unprotected sex
- For men and women without symptoms of Zika virus but who had possible exposure to Zika from recent travel or sexual contact, CDC recommends healthcare providers advise their patients wait at least 8 wk after their possible exposure before trying to get pregnant in order to minimize risk

**Table 26. Fever in the Returned Traveller**

| Illness | Geography/Timing | Pathogen | Incubation Period | Clinical Manifestations | Diagnosis | Treatment |
|---|---|---|---|---|---|---|
| **Malaria** | Africa<br>India<br>C. and S. America<br>SE Asia<br>Usually rural, night-biting mosquitoes | *Plasmodium falciparum*<br>*Plasmodium vivax*<br>*P. malaraie*<br>*P. ovale*<br>*P. knowlesi* | 7-30 d to mo or yr | Fever and flu-like illness, (shaking chills, headache, muscle aches, and fatigue)<br>Nausea/vomiting and diarrhea<br>Anemia and jaundice Plasmodium falciparum: (severe) kidney failure, seizures, mental confusion, prostration, coma, death, respiratory failure | Blood smear (thick and thin) x3<br>Rapid Diagnostic Test (with smear or PCR confirmation)<br>Antigen detection PCR (mostly a research tool) | Artesunate (for severe disease) + malarone, doxycycline, or clindamycin<br>Quinine sulfate + doxycycline or clindamycin<br>Chloroquine + primaquine |
| **Dengue** | South East Asia<br>Caribbean<br>Usually urban, day-biting mosquitoes | Dengue viruses | 3 d to 2 wk | Sudden onset of fever, headache, retro-orbital pain, myalgias, and arthralgias<br>Leukopenia<br>Thrombocytopenia Hemorrhagic manifestations (rare in travellers) | Anti-dengue IgM positivity | Symptom relief: Acetaminophen (avoid using NSAIDs because of anticoagulant properties) |
| **Typhoid (enteric fever)** | Global but mostly Indian subcontinent | *Salmonella typhi*<br>*Salmonella paratyphi* | 3 to 60 d | Sustained fever 39°-40°C (103°-104°F)<br>Abdominal pain, headache, loss of appetite, cough, constipation | Stool, urine, or blood sample positive for *S. typhi* or *S. paratyphi* | Quinolone antibiotic (e.g. ciprofloxacin), ceftriaxone, or macrolide |
| **Tick Typhus** | Mediterranean<br>South Africa<br>India | *Rickettsia* | 1 to 2 wk | Fever, headache, fatigue, muscle aches, occasionally rash<br>Eschar at site of tick bite<br>Thrombocytopenia<br>Elevated liver enzymes | Serology<br>Presence of classic tick eschar | Doxycycline |
| **TB** | Global | *M. tuberculosis* | Variable | Fever, cough, hemoptysis | CXR<br>Sputum culture and acid-fast stain | Isoniazid (INH), rifamin (RIF), pyrazinamide (PZA), ethambutamol (EMB) + Vitamin B6 |
| **Mononucleosis** | Caribbean, C. and S. America | EBV or CMV | 30 to 50 d | Malaise, fatigue, pharyngitis, lymphadenopathy, splenomegaly | Atypical lymphocytes on blood smear and positive heterophilic antibody (monospot) test | Acetaminophen or NSAIDs, fluids |
| **Zika Virus Disease** | Africa, SE Asia, S. America; spreading | Zika virus | Unknown, likely 3 to 12 d | Headache, malaise, muscle/joint pain, mild fever, rash, conjunctivitis | RT-PCR<br>Serology | Rest, fluids, analgesics/antipyretics (avoid NSAIDs until Dengue ruled out), condom use, avoid pregnancy |

# Fever of Unknown Origin

**Table 27. Classification of Fever of Unknown Origin (FUO) – Temp >38.3°C/101°F on several occasions**

| Classical FUO | Nosocomial FUO | Neutropenic FUO | HIV-associated FUO |
|---|---|---|---|
| Duration >3 wk | Hospitalized patient<br>Infection not present/ incubating on admission | Neutrophil count <500/mL or is expected to fall to that level in 1-2 d | HIV infections<br>Duration >4 wk for outpatients, >3 d for hospitalized patients |
| Diagnosis uncertain after 3 outpatient visits or 3 d in hospital or 1 wk of intensive ambulatory investigation | Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures | Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures | Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures |

**Causes of Nosocomial FUO**
**B, C, D, E**
**B**acterial and fungal infections of respiratory tract and surgical sites
**C**atheters (intravascular and urinary)
**D**rugs
**E**mboli

## Etiology of Classic FUO

- infectious causes (~30%)
  - TB: extra-pulmonary (most common), miliary, pulmonary (if pre-existing disease)
  - abscess: subphrenic, liver, splenic, pancreatic, perinephric, diverticular, pelvis, psoas
  - osteomyelitis
  - bacterial endocarditis (culture negative)
  - uncommon: viral (CMV, EBV), bacterial (brucellosis, bartonellosis), fungal (histoplasmosis, cryptococcosis), parasitic (toxoplasmosis, leishmaniasis, amoebiasis, malaria)
- neoplastic causes (~20%)
  - most commonly lymphomas (especially non-Hodgkin's) and leukemias, also multiple myeloma, myelodysplastic syndrome
  - solid tumours: RCC (most common), also breast, liver (hepatoma), colon, pancreas, or liver metastases
- collagen vascular diseases (~30%)
  - SLE, RA, rheumatic fever, vasculitis (temporal arteritis, PAN), JRA, Still's disease
- miscellaneous (~20%)
  - drugs, factitious fever
  - sarcoidosis, granulomatous hepatitis, IBD
  - hereditary periodic fever syndromes (such as familial Mediterranean fever)
  - venous thromboembolic disease: PE, DVT
  - endocrine: thyroiditis, thyroid storm, adrenal insufficiency, pheochromocytoma
- unknown in 30-50% despite detailed workup

**Drugs that may Cause Fever**
- Anti-microbials (sulfonamides, penicillins, nitrofurantoin, antimalarials)
- Anti-hypertensives (hydralazine, methyldopa)
- Anti-epileptics (barbiturate, phenytoin)
- Anti-arrythmics (quinine, procainamide)
- Anti-inflammatories (NSAIDs)
- Anti-thrombotics (ASA)
- Anti-histamines
- Anti-thyroid

## Approach to Classic FUO

- careful and repeated history: travel, environmental/occupational exposures, infectious contacts, medication history, immunizations, TB history, sexual history, past medical history, comprehensive review of systems (including symptoms that resolved before interview)
- thorough physical exam: fever pattern, rashes (skin, mucous membranes), murmurs, arthritis, lymphadenopathy, organomegaly
- initial investigations as appropriate
  - blood work: CBC and differential, electrolytes, urea, Cr, calcium profile, LFTs, ESR, CRP, muscle enzymes, RF, ANA, serum protein electrophoresis (SPEP), blood smear
  - cultures: blood (x2 sets), urine, sputum, stool C&S, O&P, other fluids as appropriate
  - serology: HIV, monospot, CMV IgM
  - imaging: CXR, abdominal imaging
- if there are diagnostic clues from any of the above steps, proceed with directed exam, biopsies or invasive testing as required, followed by directed treatment once a diagnosis is established
- if no diagnosis with the above, consider empiric therapy vs. watchful waiting
  - without intervention: patients that remain undiagnosed despite extensive workup have good prognosis
- immunocompromised hosts have increased susceptibility to infections from pathogens that are typically low virulence, commensal, or latent

# Infections in the Immunocompromised Host

## Factors that Compromise the Immune System

- general: age (very young or elderly), malnutrition
- immune disease: HIV, malignancies, asplenia (functional or anatomic), hypogammaglobulinemia, neutropenia
- DM
- iatrogenic: corticosteroids, chemotherapy, radiation treatment, anti-TNF therapy, other immunosuppressive drugs (e.g. in transplant patients)

**Table 28. Types of Immunodeficiency**

| Type | Conditions | Vulnerable To |
|---|---|---|
| **Cell-Mediated Immunity** | HIV, Hodgkin, hairy cell leukemia, cytotoxic drugs, SCID, DiGeorge syndrome | Latent viruses<br>Fungi<br>Parasites<br>Nontuberculosis mycobacterium (NTM) |
| **Humoral Immunity** | CLL, lymphosarcoma, multiple myeloma, nephrotic syndrome, protein-losing enteropathy, burns, sickle cell anemia, asplenia, splenectomy, selective Ig deficiencies, Wiskott-Aldrich syndrome | Encapsulated organisms (*S. pneumoniae, H. influenzae, N. meningitidis, Salmonella typhi*, GBS) |
| **Neutrophil Function** | Chemotherapy, myelodysplasia, paroxysmal nocturnal hemoglobinuria, radiation, cytotoxic drug therapy, C3 or C5 deficiencies, chronic granulomatous disease | Catalase-producing organisms (*Staphylococcus, Serratia, Nocardia, Aspergillus*) |

**Infections Associated with Asplenia**

- *Haemophilus influenzae* type b
- *Streptococcus pneumoniae*
- *Neisseria* meningitidis
- *Salmonella*
- Babesiosis
- Malaria
- Capnocytophaga canimorsus (dog bite)

# Febrile Neutropenia

## Definition

- fever (≥38.3°C/101°F or ≥38.0°C/100.4°F for ≥1 h) and one of:
  - ANC <0.5 OR
  - ANC <1.0 but trending down to 0.5

ANC (absolute neutrophil count) = WBC x (%neutrophils + %bands)

## Pathophysiology

- decreased neutrophil production
  - marrow: infection, aplastic/myelophthisic anemia, leukemia, lymphoma, myelodysplastic syndromes
  - iatrogenic: cancer chemotherapy, radiation, drugs
  - deficiencies: vitamin B12, folate
- increased peripheral neutrophil destruction
  - autoimmune: Felty's syndrome, SLE, antineutrophil antibodies
  - splenic sequestration

Usual signs and symptoms of infection may be diminished because neutrophils are required for a robust inflammatory response; exam and x-ray findings may be more subtle

## Epidemiology/Etiology

- most common life-threatening complication of cancer therapy
- 8 cases per 1000 cancer patients per yr in the U.S.
- causative organism identified only 1/3 of the time
- GN (especially Pseudomonas) historically most common
- GP more common now
- fungal superinfection if neutropenia prolonged or if concurrent antibiotic use (especially *Candida, Aspergillus*)
- Frequently associated with IV lines, mucosal or GI infection. *Typhlitis* (inflammation of cecum) is a rare complication, but can lead to serious infection and poor outcomes

WBC is lowest between 5-10 d after last chemotherapy cycle

## Investigations

- examine for potential sites of infection: mucositis and line infections are most common
- do NOT perform DRE; examine perianal region for perianal abscess
- blood C&S (x2 sets), urine C&S, culture all indwelling catheter ports, ± sputum C&S and nasopharyngeal swab for respiratory viruses
- CBC and differential, Cr, urea, electrolytes, AST/ALT, total bilirubin, CXR (depending on stage of disease)

## Treatment

- most hospitals have their own specific protocol so check local guidelines first; one example see Figure 16

Prophylaxis against FN with G-CSF (granulocyte colony-stimulating factor) and GM-CSF (granulocyte-macrophage colony-stimulating factor) decreases hospitalization without affecting mortality (indicated if risk of FN 20% or if FN has occurred in a previous chemotherapy cycle)

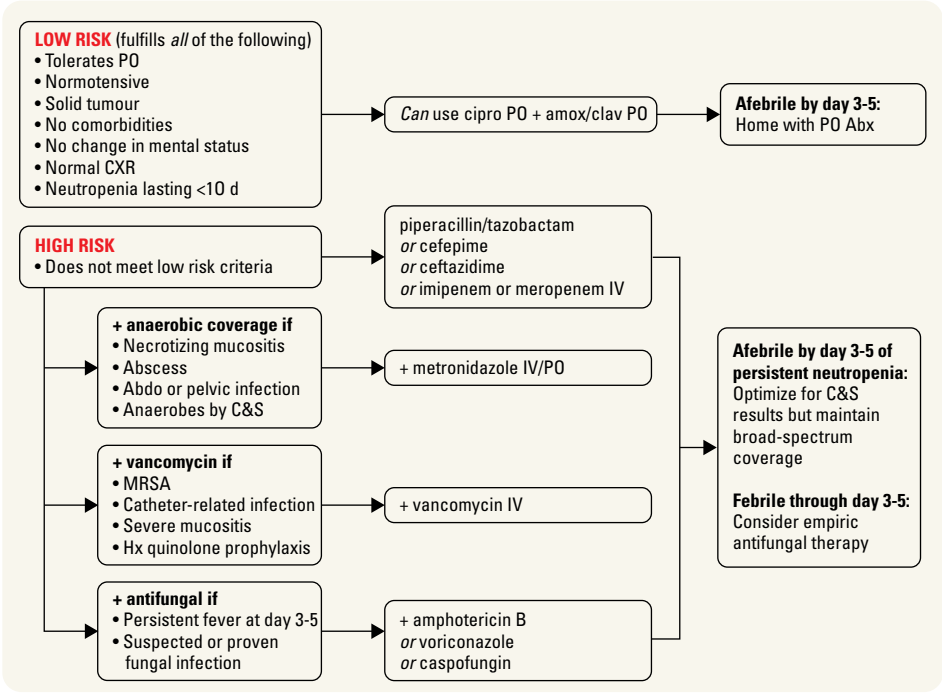



**Figure 16. Example of treatment protocol for febrile neutropenia**

# Infections in Solid Organ Transplant Recipients

- infection is a leading cause of early morbidity/mortality in transplant recipients
- infection depends on degree of immunosuppression
- common infections <1 mo post-transplant
  - bacterial infection of wound/lines/lungs, herpetic stomatitis
- common infections >1 mo post-transplant
  - viral (especially CMV, EBV, VZV)
  - fungal (especially *Aspergillus, Cryptococcus, P. jiroveci*)
  - protozoan (especially *Toxoplasma*)
  - unusual bacterial/mycobacterial infections (especially TB, *Nocardia, Listeria*)

### Prophylactic Vaccinations Given Before Transplant

- to all transplant patients: DTaP, pneumococcal, influenza, hepatitis A and B vaccines
- if low titre or poor documentation: MMR, polio, varicella vaccination (with booster 4-8 wk later)

# Immune Reconstitution Syndrome

### Definition

- a harmful inflammatory response directed against a previously acquired infection following a recovery of the immune system

### Etiology

- paradoxical worsening of a successfully or partially treated opportunistic infection
- new onset response to a previously unidentified opportunistic infection
- the majority of cases are in patients with advanced HIV or immunosuppressed patients starting anti-retroviral therapy or discontinuing immunosuppressive therapy; sudden recovery from an immunosuppressive state towards a pro-inflammatory state directed towards subclinical infection results in fever and inflammation
- can occur in response to multiple infections
  - *Mycobacteria* (tuberculosis, avium complex)
  - *Cryptococcus*
  - *Pneumocystis*
  - *Toxoplasma*
  - HBV and HCV
  - herpes viruses (VZV reactivation, HSV, CMV)
  - JC virus (progressive multifocal leukoencephalopathy)
  - *Molluscum contagiosum*
- clinical features are dependent on the type and location of the pre-existing infection
- thought to be worse with quick increase in CD4 count and with lower pre-treatment CD4 count
- non-HIV conditions with documented IRS: solid organ transplant recipients, post-partum women, neutropenic patients, anti-TNF therapy

### Epidemiology
- in HIV-positive patients starting ART, IRS reported to affect ~10%

### Investigations
- IRS is a diagnosis of exclusion
- rule out drug reaction, medication non-adherence, drug resistance

### Treatment
- continue ARV therapy in HIV-positive patients with mild-moderate symptoms, but consider discontinuation if symptoms are life-threatening or potentially irreversible
- treat underlying infection; initiate treatment for some infections prior to ARV initiation
- consider starting corticosteroids/NSAIDs to decrease inflammatory response

# A Simplified Look at Antibiotics

- general overview, see Table 29, ID46 for more details

**1. Penicillins**

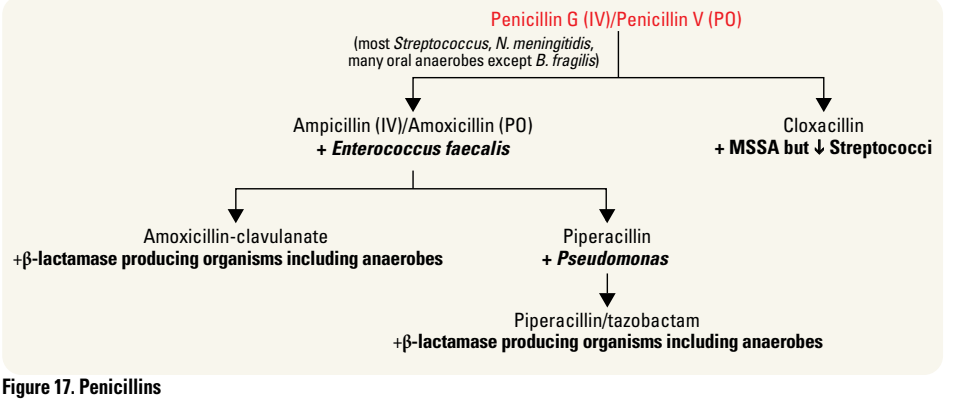



**Figure 17. Penicillins**

**2. Cephalosporins (PO/IV)**
- 1st generation: cephalexin/cefazolin (mostly GP, some GN) or cefadroxil
- 2nd generation: cefuroxime/cefprozil (some GP and some GN, *anaerobes)
- 3rd generation: cefixime/cefotaxime, ceftriaxone (good Streptococcal coverage, mostly GN), and ceftazidime (no GP, mostly GN, *Pseudomonas*)
- 4th generation: --/cefepime (most GP, *most* GN, *Pseudomonas*), ceftaroline (for MRSA)

**3. Aminoglycosides (GN aerobic bacilli include *Pseudomonas*)**
- gentamicin
- tobramycin
- amikacin
- plazomicin

**4. Macrolides (GP, *Haemophilus*, and atypical bacteria [*Legionella, Chlamydophila, Mycoplasma*])**
- erythromycin
- clarithromycin
- azithromycin

**5. Fluoroquinolones (GN – although resistance becoming a huge problem)**
- ciprofloxacin (+ *Pseudomonas*)
- norfloxacin (for spontaneous bacterial peritonitis (SBP) prophylaxis )
- "respiratory" fluoroquinolones (some GP, GN, "atypicals", *Legionella, Mycoplasma, Chlamydophila, Mycobacteria*)
  - levofloxacin
  - moxifloxacin (has some anaerobic coverage)

**6. Carbapenems (broad coverage: GP, GN, and anaerobes)**
- imipenem (+ *Pseudomonas*)
- meropenem (+ *Pseudomonas*)
- ertapenem

**7. Others**
- doxycycline/tetracycline/minocycline (GP, syphilis, *Chlamydophila, Rickettsia, Mycoplasma*)
- tigecycline (for resistant GP infections, GN, anaerobes, *Chlamydophila, Rickettsia, Mycoplasma*)
- vancomycin (all GP and *C. difficile* – the oral form for)
- linezolid (for resistant GP infections)
- daptomycin (for resistant GP infections)
- clindamycin (most GP, GN anaerobes)
- TMP/SMX (most *S. aureus* including: MRSA, GN aerobes, *Pneumocystis*)
- nitrofurantoin (GN bacilli, *S. saprophyticus, Enterococcus*)
- metronidazole (anaerobes including: *Bacteroides* sp., *C. difficile; Trichomonas, Entamoeba*)

# Antimicrobials

## Antibiotics

- empiric antibiotic therapy
  - choose antibiotic(s) to cover for most likely and lethal organisms for the type of infection prior to obtaining laboratory results (usually reserved for serious infections)
  - adjust antibiotic(s) based on C&S and clinical response
- if causative organism identified, use antibiotic to which organism is susceptible
- if causative organism not identified, re-evaluate need for ongoing antimicrobial therapy (and continue with empiric antibiotic(s) if indicated)

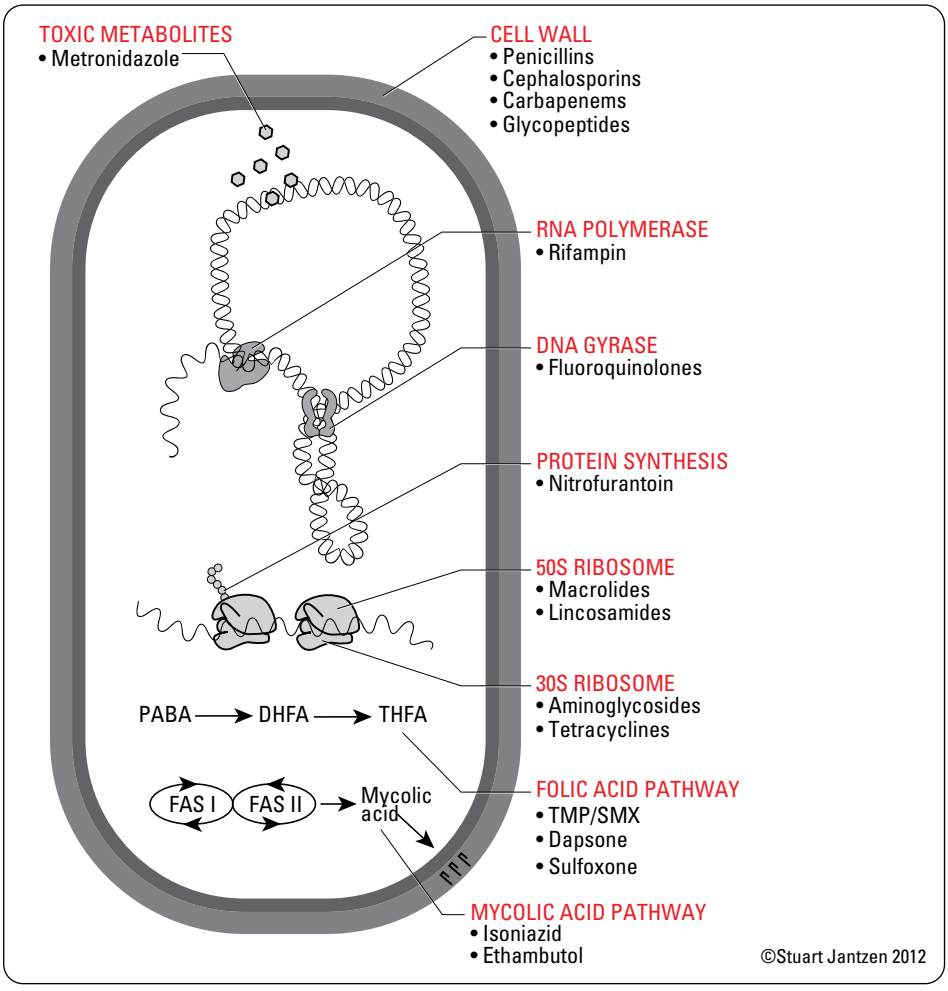



**Figure 18. Mechanism of action of antibiotics**

**Reasons for Combination Therapy**
- Polymicrobial infection
- Empiric therapy pending culture results
- Synergy for difficult to treat pathogens (e.g. *Enterococcus* spp. causing endocarditis)
- To prevent emergence of resistance

| Bactericidal Antibiotics | Bacteriostatic Antibiotics |
|---|---|
| "**V**ery **F**inely **P**roficient **A**t **CC**ell **M**ur**D**er" | "**ECST**a**T**i**C**" |
| **V**ancomycin | **E**rythromycin (and other macrolides) |
| **F**luoroquinolones | **C**lindamycin |
| **P**enicillin | **S**ulfamethoxazole |
| **A**minoglycosides | **T**rimethoprim |
| **C**ephalosporins | **T**etracyclines |
| **C**arbapenems | **C**hloramphenicol |
| **M**etronidazole | |
| **D**aptomycin | |

## Table 29. Antibiotics

| Class and Drugs | Coverage | Mechanism of Action | Adverse Effects | Indications | Contraindications |
|---|---|---|---|---|---|
| **CELL WALL INHIBITORS** | | | | | |
| **Penicillins** | | | | | |
| Benzyl penicillin<br>- penicillin G IV/IM<br>- penicillin V PO | GP except *Staphylococcus, Enterococcus, N. meningitidis*,<br>Oral anaerobes<br>Syphilis | Bactericidal: β-lactam inhibits cell wall synthesis by binding penicillin binding protein (PBP) preventing cross-linking of peptidoglycan | Immediate allergy (IgE): anaphylaxis, urticaria<br>Late-onset allergy (IgG): urticaria, rash, serum sickness<br>Interstitial nephritis<br>Dose related toxicity: seizures<br>Diarrhea | Mild to moderately severe infections caused by susceptible organisms including: actinomycosis, streptococcal pharyngitis, streptococcal skin and soft tissue infections, pneumococcal pneumonia, syphilis | Hypersensitivity to penicillin cov? |
| Aminopenicillin<br>- ampicillin IV<br>- amoxicillin PO (Amoxil®) | Same as penicillin AND<br>*Enterococcus*<br>*Listeria*<br>Some strains of:<br>*H. influenzae,*<br>*E. coli,*<br>*K. pneumoniae* | See above | See above | Bacterial meningitis and endocarditis (IV ampicillin), acute otitis media (AOM), streptococcal pharyngitis, sinusitis, acute exacerbations of COPD, part of multidrug therapy for *H. pylori* treatment, Lyme disease, pneumococcal pneumonia; UTI (amoxicillin and ampicillin) for most enterococci and susceptible Gram negative pathogens | Hypersensitivity to penicillin or β-lactam antibiotics |
| Isoxazyolyl penicillin<br>- cloxacillin<br>- methicillin<br>- nafcillin<br>- oxacillin | Methicillin-sensitive *Staphylococcus aureus*; streptococci | See above | See above | Bacterial infections caused by staphylococci and streptococci including skin and soft-tissue infections | Hypersensitivity to cloxacillin or any penicillin |
| β-lactam/β-lactamase inhibitor combinations<br>- amoxicillin-clavulanate (Clavulin®, Augmentin®)<br>- piperacillin/tazobactam (Tazocin®) | Same as penicillin AND<br>*Staphylococcus*<br>*H. influenzae*<br>*Enterococcus*<br>Anaerobes (oral and gut) | β-lactamase produced by certain bacteria inactivate β-lactams Lactamase inhibitors prevent this process, preserving antibacterial effect of β-lactams | See above | Various β-lactamase producing bacteria, Clavulin® sensitive bacteria including RTI, sinusitis, AOM, skin and soft tissue infections, UTI, and severe intra-abdominal and pelvic infections | Hypersensitivity to penicillin or cephalosporin<br>History of Clavulin®-associated jaundice or hepatic dysfunction |
| **Cephalosporins** | | | | | |
| **PO**<br>1°<br>cephalexin (Keflex®) | **IV**<br>cefazolin (Ancef®) | **GP**<br>Good with the exception of *Enterococcus* and MRSA | **GN**<br>*E. coli, Klebsiella, Proteus, H. influenzae* (not all isolates) | Bactericidal: β-lactam inhibits PBP, prevents cross-linking of peptidoglycan, less susceptible to penicillinases | 10% penicillin allergy cross-reactivity | Skin and soft tissue infections, prevention of surgical site infections (cefazolin); infections caused by susceptible organisms (especially *Staph* and *Strep* infections) | Hypersensitivity to cephalosporins or other β-lactam antibiotics |
| 2°<br>cefuroxime (Ceftin®)<br>cefprozil (Cefzil®) | cefuroxime (Zinacef®)<br>cefoxitin[A] | Weaker activity than 1° | More coverage than 1° ([A]includes anaerobes) | See above | See above | Upper and lower respiratory tract infections; pneumococcal pneumonia; soft tissue infections | See above |
| 3° cefixime (Suprax®) | ceftriaxone (Rocephin®)<br>cefotaxime (Claforan®)<br>ceftazidime[B] (Fortaz®) | *S. aureus* + streptococcal coverage (cefotaxime and ceftriaxone) especially *S. pneumoniae* | Broad coverage ([B]includes *Pseudomonas* for ceftazidime only) | See above | ~1% penicillin allergy cross-reactivity | Community-acquired pneumonia (cefotaxime, ceftriaxone), gonorrhea (use ceftriaxone), community-acquired bacterial meningitis (ceftriaxone, cefotaxime); abdominal and pelvic infections (cefotaxime or ceftriaxone in combination with metronidazole); once-daily administration makes ceftriaxone convenient for outpatient IV therapy | Severe hypersensitivity (Type I) to other β-lactam antibiotics |
| 4° | cefepime (Maxipine®) | Broad spectrum | Broad coverage including *Pseudomonas* | See above | See above | Empiric therapy for febrile neutropenia | See above |

**Table 29. Antibiotics** (continued)

| Class and Drugs | Coverage | Mechanism of Action | Adverse Effects | Indications | Contraindications |
|---|---|---|---|---|---|
| **CELL WALL INHIBITORS** | | | | | |
| **Carbapenems** | | | | | |
| imipenem (Primaxin®) | GP except MRSA GN including *Pseudomonas* + *Enterobacter*, ESBLs, anaerobes | β-lactam inhibits PBP and prevents cross-linking of peptidoglycan | Penicillin allergy cross-reactivity<br>Seizures | Treatment of infections caused by GNB producing extended-spectrum β-lactamases, serious infections caused by susceptible organisms | Hypersensitivity to imipenem<br>Lowers seizure threshold compared to carbapenems |
| meropenem (Merrem®) | See above; does not cover *Enterococcus* | See above | See above | See above | Hypersensitivity to β-lactams |
| ertapenem (Invanz®) | GP except *Enterococcus*, MRSA GN including *Enterobacter* (but not *Pseudomonas*), anaerobes | See above | See above | See above; once-daily administration makes it convenient for outpatient IV therapy | Hypersensitivity to β-lactams |
| **Glycopeptides** | | | | | |
| Vancomycin (Vancocin®) | GP including MRSA, not VRE<br>*C. difficile* if PO | Glycopeptide sterically inhibits cell wall synthesis | Red Man Syndrome<br>Nephrotoxicity<br>Ototoxicity<br>Thrombocytopenia | Severe or life-threatening GP infections, patients with β-lactam allergy<br>May only be taken orally for severe *C. difficile* infection | Hypersensitivity to vancomycin |
| **PROTEIN SYNTHESIS INHIBITORS (50S RIBOSOME)** | | | | | |
| **Macrolides** | | | | | |
| erythromycin (Erybid®, Eryc®)<br>*This agent is rarely used due to GI upset | GP except *Enterococcus*<br>GN: *Legionella, B. pertussis*<br>"Atypicals": *Chlamydophila, Mycoplasma* | Binds to 50S ribosomal subunit inhibiting protein synthesis | GI upset<br>Acute cholestatic hepatitis<br>Prolonged QT | Susceptible RTI, pertussis, diphtheria, Legionnaires' disease, skin and soft tissue infections | Hypersensitivity to erythromycin<br>Concurrent therapy with astemizole, terfenadine |
| clarithromycin (Biaxin®) | See above, some mycobacteria | See above | See above | Susceptible RTI, skin infections, non-tuberculous mycobacterial infections, part of multidrug therapy for *H. pylori* treatment | Hypersensitivity to macrolides |
| azithromycin (Zithromax®) | See above, some mycobacteria | See above | See above | Susceptible RTI, acute exacerbations of COPD, community-acquired pneumonia, skin infections, *Campylobacter* infections if treatment indicated, chlamydia | Hypersensitivity to macrolides |
| **Lincosamides** | | | | | |
| clindamycin (Dalacin®) | GP except *Enterococcus*, most community-acquired MRSA<br>Anaerobes | Inhibits peptide bond formation at 50S ribosome | Pseudomembranous colitis and *C. difficile*<br>GI upset | Treatment of suspected or proven infections caused by GP, anaerobes including skin and skin structure infections, oropharyngeal infections, in combination with GN coverage for intra-abdominal and pelvic infections | Hypersensitivity to clindamycin<br>Infants <30 d |
| chloramphenicol | GP GN Anaerobes | Inhibits peptidyl transferase action of tRNA at 50S ribosome | Aplastic anemia<br>Grey Baby Syndrome | Serious infections by susceptible organisms when suitable alternatives are not available including meningococcal disease in patients with anaphylaxis to β-lactams | Hypersensitivity to chloramphenicol |
| linezolid (Zyvoxam®) | GP including VRE + MRSA | Binds 50S ribosome and prevents functional 70S initiation complex | HTN (acts as MAOI)<br>Risks with prolonged use: myelosuppression, optic neuropathy, peripheral neuropathy | Vancomycin-resistant *Enterococcus faecium* infections including intra-abdominal, skin and skin structure, and urinary tract infections, MRSA infections as outpatient therapy | Hypersensitivity to linezolid |

**Table 29. Antibiotics** (continued)

| Class and Drugs | Coverage | Mechanism of Action | Adverse Effects | Indications | Contraindications |
|---|---|---|---|---|---|
| **PROTEIN SYNTHESIS INHIBITORS (30S RIBOSOME)** | | | | | |
| **Aminoglycosides** | | | | | |
| gentamicin<br>tobramycin<br>amikacin (Amikin®) | GN (includes *Pseudomonas*) | Binds 30S subunit of ribosome inhibiting protein synthesis | Nephrotoxicity (reversible)<br>Vestibular and ototoxicity (irreversible)<br>Vestibular toxicity is the most important aminoglycoside toxicity | GN infections when alternatives do not exist, UTIs, used in low doses for synergy with β-lactams or with vancomycin for the treatment of serious enterococcal infections | Pre-existing hearing loss and renal dysfunction |
| **Tetracyclines** | | | | | |
| tetracycline (Apo-Tetra®, Nu-TetraT®)<br>minocycline (MinocinT®)<br>doxycycline (Doxycin®)<br>tigecycline (Tygacil®) | GP<br>Anaerobes<br>"Atypicals": *Chlamydophila, Mycoplasma, Rickettsia, Borrelia burgdorferi*<br>*Treponema*<br>Malaria prophylaxis (doxycycline)<br>Tigecycline has activity against MRSA, VRE, and ESBL-producing *E. coli/K. pneumoniae* | Binds 30S subunit of ribosome inhibiting protein synthesis | GI upset<br>Hepatotoxicity<br>Fanconi's syndrome<br>Photosensitivity<br>Teratogenic<br>Yellow teeth and stunted bone growth in children | Rickettsial infections, *Chlamydophila*, acne (tetracycline, minocycline), PID (step-down), malaria prophylaxis (doxycycline) | Severe renal or hepatic dysfunction<br>Pregnancy or lactation<br>Children under 8 yr |
| **TOPOISOMERASE INHIBITORS** | | | | | |
| **Fluoroquinolones (FQs)** | | | | | |
| ciprofloxacin (Cipro®)<br>norfloxacin (Apo-Norflox®)<br>ofloxacin (Floxin®)<br>Respiratory FQs:<br>levofloxacin (Levaquin®)<br>moxifloxacin (Avelox®) | Variable GP activity<br>GN (includes *Pseudomonas*)<br>Atypicals<br>Levofloxacin and Moxifloxacin cover *S. pneumoniae*<br>Moxifloxacin also has additional anaerobic coverage | Inhibits DNA gyrase | Headache, dizziness<br>Allergy<br>Seizures<br>Prolonged QT<br>Dysglycemia (levofloxacin, moxifloxacin)<br>Tendonitis<br>Tendon rupture | Upper and lower RTI (not ciprofloxacin unless susceptible organism isolated), UTI, prostatitis (not moxifloxacin), bone and joint infections for susceptible organisms, skin and soft tissue infections (levofloxacin, moxifloxacin), infectious diarrhea, meningococcal prophylaxis, intra-abdominal infections (moxifloxacin, ciprofloxacin in combination with metronidazole or clindamycin), febrile neutropenia prophylaxis (ciprofloxacin, levofloxacin) or ciprofloxacin in combination with amoxicillin-clavulanate low management of "low-risk" febrile neutropenia | |
| **OTHER** | | | | | |
| **Rifampin** | GP cocci<br>*N. meningitidis*<br>*H. influenzae*<br>*Mycobacteria* | Inhibits RNA polymerase | Hepatic dysfunction, P450 enzyme induction<br>Orange tears/saliva/urine | Part of multidrug treatment for active TB, alone for treatment of latent TB, part of multidrug treatment of other mycobacterial infections, endocarditis involving prosthetic valve or other prosthetic device infections in combination with other antibiotic agents, prophylaxis for those exposed to people with *N. meningitidis* or HiB meningitis | Jaundice<br>Not to be used as monotherapy (except for prophylaxis) |
| **Metronidazole** (Flagyl®) | Anaerobes Protozoa | Forms toxic metabolites in bacterial cell which damage microbial DNA | Disulfiram-type reaction with EtOH<br>Seizures<br>Peripheral neuropathy | Protozoal infections (trichomoniasis, amoebiasis, giardiasis), bacterial vaginosis, anaerobic bacterial infections | |
| **Daptomycin** | GP, including MRSA and VRE | Hypothesized to bind to cell wall and form channels leading to intracellular $K^+$ depletion | Skeletal muscle injury at high doses (elevated CPK) Peripheral neuropathy | Bacteremia, endocarditis, skin and soft tissue, and other infections due to resistant GP infections including MRSA and VRE | Known hypersensitivity<br><br>Inactivated by surfactant, therefore not used in MRSA pneumonia Tx |

**Table 29. Antibiotics** (continued)

| Class and Drugs | Coverage | Mechanism of Action | Adverse Effects | Indications | Contraindications |
|---|---|---|---|---|---|
| **ANTI-METABOLITE** | | | | | |
| **Trimethoprim-Sulfamethoxazole (TMP/SMX)** (Septra®, Bactrim®) | GP, especially *S. aureus* (including most MRSA)<br>GN: enteric<br>*Nocardia*<br>Other: *Pneumocystis, Toxoplasmosis* | Inhibits folic acid pathway (TMP inhibits DHFR and SMX competes with PABA) | Hepatitis<br>Stevens-Johnson syndrome<br>Bone marrow suppression<br>Hyperkalemia<br>Drug toxicity (increases free levels of many drugs, including glyburide, warfarin) | Susceptible UTI, RTI, GI infections, skin and soft tissue infections caused by staphylococcal species, treatment and prophylaxis of *P. jiroveci* pneumonia | Hypersensitivity to TMP-SMX, sulfa drugs |
| **nitrofurantoin** (MacroBID®, (Macrodantin®) | *Enterococcus, S. saprophyticus*<br>GN (coliforms) | Reactive metabolites inhibit ribosomal protein synthesis | Cholestasis, hepatitis<br>Hemolysis if G6PD deficiency<br>Interstitial lung disease with chronic use | Lower UTI; not pyelonephritis or bacteremia | Hypersensitivity to nitrofurantoin<br>Anuria, oliguria, or significant renal impairment<br>Pregnant patients during labour and delivery or when labour imminent<br>Infants <1 mo of age |
| **ANTI-MYCOBACTERIALS** | | | | | |
| isoniazid (INH) | *Mycobacteria* | Inhibits mycolic acid synthesis | Hepatotoxicity<br>Hepatitis<br>Drug-induced SLE<br>Peripheral neuropathy | Part of multidrug treatment for active TB, alone for treatment of latent TB | Drug-induced hepatitis or acute liver disease |
| rifampin (RIF) | *Mycobacteria* | Inhibits RNA polymerase | Hepatotoxicity P450 enzyme inducer<br>Orange tears, saliva, urine | Part of multidrug treatment for active TB, alone for treatment of latent TB, part of multidrug treatment of other mycobacterial infections | Jaundice<br>Not to be used monotherapy (except for prophylaxis) |
| ethambutol | *Mycobacteria* | Inhibits mycolic acid synthesis | Loss of central and colour vision<br>Neuropathy | Part of multidrug treatment for active TB and other mycobacterial infections | Renal failure |
| pyrazinamide (PZA) | *Mycobacteria* | Unknown | Hepatotoxicity<br>Gout<br>Gastric irritation | Part of multidrug treatment for active TB | Severe hepatic damage or acute liver disease<br>Patients with acute gout |
| **SULFONES** | | | | | |
| dapsone<br>sulfoxone | *M. leprae, P. jiroveci, Toxoplasma* | Inhibit folic acid synthesis by competition with PABA | Rash<br>Drug fever<br>Agranulocytosis | Part of multidrug treatment for *M. leprae*, part of treatment for *P. jiroveci* pneumonia (with TMP), *P. jiroveci* pneumonia prophylaxis, toxoplasmosis prophylaxis with pyrimethamine | |

**Table 30. Antibiotics for Selected Bacteria**

| *Pseudomonas* | *S. aureus* | *Enterococcus* | *H. influenzae* | Anaerobes |
|---|---|---|---|---|
| ciprofloxacin | cloxacillin (MSSA) | ampicillin | amoxicillin-clavulanate | metronidazole |
| gentamicin, tobramycin amikacin | 1° cephalosporin (MSSA) | amoxicillin | 2°/3° cephalosporin | clindamycin |
| piperacillin/ tazobactam | clindamycin | vancomycin | macrolides (clarithromycin, azithromycin) | amoxicillin-clavulanate |
| ceftazidime | cotrimoxazole (including MRSA) | nitrofurantoin (lower UTI) | levofloxacin | cefoxitin |
| cefipime | vancomycin (including MRSA) | linezolid for VRE | moxifloxacin | piperacillin/tazobactam |
| meropenem, imipenem | linezolid (including MRSA) | daptomycin for VRE | | moxifloxacin |
| | daptomycin (including MRSA) | tigecycline for VRE | | ertapenem, imipenem, meropenem |
| | tigecycline (including MRSA) | | | |
| | doxycycline (MSSA/MRSA) | penicillin | | |
| | | imipenem | | |



**Rifampin**
- Good adjunct for treating prosthetic device infection (bacterial biofilm)
- Always used in combination with other antibiotics to reduce emergence of resistance

# Antivirals

**Table 31. Antivirals**

| Class and Drugs | Coverage | Mechanism of Action | Adverse Effects | Contraindications |
|---|---|---|---|---|
| **ANTI-HERPESVIRUS** | | | | |
| acyclovir<br>valacyclovir (Valtrex®)<br>(prodrug of acyclovir) | HSV-1,2<br>VZV | Guanosine analog inhibits viral DNA polymerase | PO well-tolerated<br>IV: nephrotoxicity, CNS | Hypersensitivity to acyclovir or valacyclovir |
| famciclovir (Famvir®)<br>penciclovir | HSV-1,2<br>VZV | See above | Headache, nausea | Hypersensitivity to famciclovir or penciclovir |
| ganciclovir (Cytovene®)<br>valganciclovir (prodrug of ganciclovir) | CMV<br>HSV-1,2, VZV, HHV-6, EBV | See above | Heme: neutropenia, thrombocytopenia, anemia | Hypersensitivity to ganciclovir or valganciclovir<br>Possible cross-hypersensitivity between acyclovir and valacyclovir |
| Foscarnet | CMV<br>Acyclovir-resistant HSV, VZV | Pyrophosphate analog inhibits viral DNA polymerase | Nephrotoxicity<br>Anemia<br>Electrolyte disturbance | Hypersensitivity to foscarnet |
| **OTHER ANTIVIRALS** | | | | |
| (pegylated) interferon-α-2a or-2b | Chronic hepatitis B or C HPV | Inhibits viral protein synthesis | "Flu-like" syndrome<br>Depression<br>Bone marrow suppression | Hypersensitivity to any interferon<br>Cannot use in combination with ribavirin if renal impairment |
| ribavirin (Virazole®) | Chronic hepatitis C RSV Lassa fever | Guanosine analog with multiple postulated mechanisms of action | Hemolytic anemia<br>Rash, conjunctivitis<br>Highly teratogenic | Pregnancy, women who may become pregnant or their partners<br>Renal impairment |
| Cidofovir | Adenovirus<br>CMV retinitis<br>Acyclovir and foscarnet resistant HSV | Deoxycitidine analogue Inhibits DNA synthesis | Nephrotoxicity (proximal tubule dysfunction) | Renal failure; probenecid can reduce renal toxicity |
| lamivudine (Epivir®) | Chronic hepatitis B HIV | See *HIV and AIDS*, ID25 | See *HIV and AIDS*, ID25 | See *HIV and AIDS*, ID25 |
| Tenofovir | Chronic hepatitis B HIV | See *HIV and AIDS*, ID25 | See *HIV and AIDS*, ID25 | See *HIV and AIDS*, ID25 |
| Neuraminidase inhibitors:<br>zanamivir (Relenza®)<br>oseltamivir (Tamiflu®) | Influenza A and B: treatment and prophylaxis | Inhibits neuraminidase, an enzyme required for release of virus from infected cells and prevention of viral aggregation | GI: nausea/vomiting, diarrhea<br>Bronchospasm in zanamavir | Hypersensitivity to the neuraminidase inhibitors |

# Antifungals

**Table 32. Antifungals**

| Class and Drugs | Coverage | Mechanism of Action | Adverse Effects | Contraindications |
|---|---|---|---|---|
| **POLYENES** | | | | |
| amphotericin B | Endemic mycoses:<br>Histoplasmosis<br>Blastomycosis<br>Coccidioidomycosis<br>Pulmonary:<br>Aspergillosis<br>CNS:<br>*Cryptococcus* | A polyene antimicrobial: inserts into fungal cytoplasmic membrane causing altered membrane permeability and cell death | Nephrotoxicity<br>Hypo/hyperkalemia<br>Infusion reactions: chills, fevers, headache<br>Peripheral phlebitis | Renal impairment |
| nystatin (oral, topical) | Candidiasis: mucocutaneous, GI, oral (thrush), vaginal | See above<br>Not absorbed from the GI tract | GI: nausea/vomiting, diarrhea<br>Highly toxic if given IV | |
| **IMIDAZOLES** | | | | |
| clotrimazole (Canesten®) | Oral and vulvovaginal candidiasis Dermatomycoses | All azoles: inhibit ergosterol synthesis and thereby alter fungal cell membrane permeability | Pruritis, skin irritation | |
| miconazole (Monistat®, Micozole®) | Vulvovaginal candidiasis<br>Dermatomycoses | | Vaginal burning<br>Nausea/vomiting | |
| ketoconazole (Nizoral®) | Dermatomycoses<br>Seborrheic dermatitis | | Pruritis, skin irritation GI nonspecific Results in decreased androgen and testosterone synthesis | Cross-sensitivity with other azoles possible<br>Hepatic dysfunction<br>Pregnant women or those that may become pregnant |

**Table 32. Antifungals** (continued)

| Class and Drugs | Coverage | Mechanism of Action | Adverse Effects | Contraindications |
|---|---|---|---|---|
| **TRIAZOLES** | | | | |
| fluconazole (Diflucan®) | Candida infections (mucosal and invasive)<br>Cryptococcal meningitis (step-down therapy) | All azoles: inhibit ergosterol synthesis and thereby alter fungal cell membrane permeability | Elevated liver enzymes GI nonspecific | Cross-sensitivity with other azoles unknown |
| itraconazole (Sporanox®) | Sporotrichosis Onychomycoses<br>Endemic mycoses:<br>Histoplasmosis<br>Blastomycosis<br>Coccidioidomycosis | | Elevated liver enzymes Rash GI nonspecific HTN Hyperkalemia Peripheral edema | Cross-sensitivity with other azoles unknown<br>Severe ventricular dysfunction |
| voriconazole (Vfend®) | Aspergillosis<br>Candidiasis | | Visual disturbance (30%)<br>Hepatotoxicity<br>Cutaneous photosensitivity<br>Cutaneous squamous cell carcinoma with long-term use in immunosuppressed patients<br>Prolonged QT Periostitis<br>Neurologic toxicity | Cross-sensitivity with other azoles unknown<br>May avoid or alter doses if co-administered with other CYP3A4 substrates, rifampin, carbamazepine, long-acting barbiturates, ritonavir, efavirenz, sirolimus, rifabutin, ergot alkaloids |
| posaconazole (Posanol®, Noxafil®) | Candidiasis<br>Aspergillosis<br>Mucormycosis | | Elevated liver enzymes<br>Headache<br>Prolonged QT | Coadministration of cisapride, ergot alkaloids, pimozide, quinidine, or sirolimus |
| **ALLYLAMINES** | | | | |
| terbinafine (Lamisil®) | Dermatomycoses<br>Onychomycoses | Inhibits enzyme needed for ergosterol synthesis | Rash, local irritation GI nonspecific, transaminitis | Active liver disease |
| **ECHINOCANDINS** | | | | |
| caspofungin<br>micafungin<br>anidulafungin | Refractory aspergillosis, candidemia (azole-resistant) | Inhibits 1-3 β-D-glucan synthesis (needed for fungal cell wall) | Hepatotoxicity Infusion and injection site reactions | |

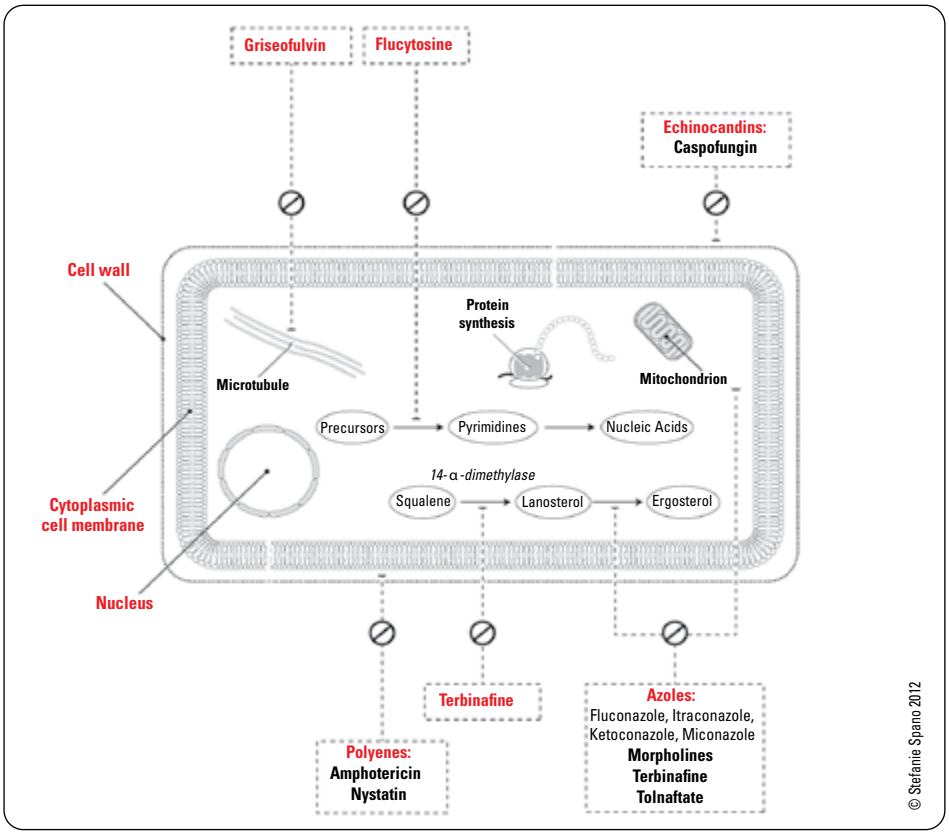



**Figure 19. Mechanism of action of antifungals**

# Antiparasitics

**Table 33. Antiparasitics**

| Class and Drugs | Coverage | Mechanism of Action | Adverse Effects | Contraindications |
|---|---|---|---|---|
| **ANTIMALARIALS** | | | | |
| chloroquine | Malaria: treatment of erythrocytic phase of all five species of *Plasmodium* that infect humans Note: High resistance of *P. falciparum* and *P. vivax* in certain geographic areas | Inhibits parasite heme polymerase | CNS: blurred vision, retinopathy, dizziness<br>Nonspecific GI (rare with prophylaxis) | Hypersensitivity to chloroquine or other 4-aminoquinoline<br>Retinal or visual field changes due to 4-aminoquinoline |
| quinine | Malaria: treatment of all five species of *Plasmodium* that infect humans, including chloroquine-resistant *P. falciparum* | | Cinchonism: ears (tinnitus, vertigo), eyes (visual disturbance), GI (nausea/vomiting, diarrhea), CNS (headache, fever)<br>Hypoglycemia | Hypersensitivity to quinine, may have cross-sensitivity with quinidine<br>Patients with G6PD deficiency, tinnitus, optic neuritis, hypoglycemia, history of blackwater fever or thrombocytopenic purpura due to quinine use |
| mefloquine (Lariam®) | Malaria: prophylaxis | | CNS/Psych: irritability, nightmares, psychoses, suicide, depression, seizures, headache | History of seizures, psychosis, severe anxiety or depression |
| primaquine | Malaria: treatment of liver hypnozoites of *P. vivax* and *P. ovale*; prophylaxis of all *Plasmodium* spp. *Pneumocystis jiroveci* (with clindamycin) | Interferes with mitochondrial function | Hemolytic anemia in G6PD deficient<br>GI upset (take with food) | GI nonspecific<br>G6PD deficiency<br>Concurrent or recent use of quinacrine<br>Pregnancy |
| atovaquone/proguanil (Malarone®) | Malaria: treatment and prophylaxis of *P. falciparum* | Inhibits mitochondrial electron transport and dihydrofolate reductase | Nausea/vomiting, anorexia, diarrhea, abdominal pain (take with food) | Hypersensitivity to atovaquone or proguanil<br>Severe renal impairment |
| artemisinin derivatives (artemether, artesunate, etc.)<br>Note: marketed primarily in endemic countries | Malaria: treatment of all *Plasmodium* spp.<br>Severe malaria (IV artesunate)<br>Typically used in combination with a longer-acting agent from above | Binds iron, leading to formation of free radicals that damage parasite proteins | Transient neurologic deficits (nystagmus, balance disturbance)<br>Transient neutropenia (at high doses of oral artesunate)<br>Delayed hemolysis | Hypersensitivity to artemisinins |
| **OTHER ANTI-PROTOZOAL** | | | | |
| iodoquinol (Diodoquin®) | Amoebiasis: *E. histolytica, Dientamoeba fragilis, Balantidium coli, Blastocystis hominis* | Contact amoebicide that acts in intestinal lumen by uncertain mechanism | GI: nausea/vomiting, diarrhea, abdominal pain CNS: headache, seizures, encephalitis | Hypersensitivity to any 8-hydroxy-quinoline or iodine<br>Patients with hepatic damage or optic neuropathy<br>Pregnancy |
| metronidazole | Amoebiasis, *T. vaginalis,* giardiasis, *D. fragilis* | See *Antibiotics*, ID48 | | |
| nitazoxanide | *Cryptosporidium*, giardiasis, cyclosporiasis | Interferes with parasite anaerobic metabolism | Nausea/vomiting, diarrhea, abdominal pain, headache | Hypersensitivity to nitazoxanide |
| **ANTI-HELMINTHICS** | | | | |
| praziquantel | *Schistosomiasis* and other flukes<br>Tapeworms | Increases $Ca^{2+}$ permeability of helminth cell membrane, causing paralysis and detachment | Nausea/vomiting, fever, dizziness | Ocular cysticercosis |
| albendazole | Intestinal roundworms<br>*Neurocysticercosis*<br>*Echinococcus*<br>Hydatid disease | Inhibits glucose uptake into susceptible parasites | Elevated liver enzymes<br>Alopecia<br>GI nonspecific<br>Agranulocytosis | Pregnancy<br>Ocular cysticercosis or intraventricular cysticercosis |
| mebendazole (Vermox®) | Intestinal roundworms: pinworm, whipworm, hookworm, roundworm (e.g. *Ascaris*) | Inhibits microtubule formation and glucose uptake | Nonspecific GI | Pregnancy, infants |
| ivermectin | *Strongyloidiasis*<br>*Onchocerciasis*<br>Scabies | Interferes with polarization of nerve and muscles cells in susceptible parasites leading to paralysis | Nausea, bloating, diarrhea, myalgias, lightheadedness, headache | Hypersensitivity to ivermectin<br>Pregnancy |
| diethylcarbamazine | *Wuchereria bancrofti*<br>*Loa loa* | | Anorexia, nausea/vomiting, headache, drowsiness, encephalitis, retinal hemorrhage<br>Mazzotti reaction if coinfected with onchocerciasis | Pregnancy<br>Onchocerciasis |

# Quick Reference: Common Infections and Their Antibiotic Management

- see Family Medicine, FM51

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# MG Medical Genetics

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# Acronyms

| | |
|---|---|
| CF | cystic fibrosis |
| CNV | copy number variant |
| FISH | fluorescence in situ hybridization |
| FTS | first trimester screening |
| GA | gestational age |
| GSD | glycogen storage disease |
| IPS | integrated prenatal screening |
| MSUD | maple syrup urine disease |
| NGS | next generation sequencing |
| NIPT | non-invasive prenatal testing |
| ONTD | open neural tube defect |
| PKU | phenylketonuria |
| SCID | severe combined immunodeficiency |
| US | ultrasound |
| WES | whole exome sequencing |

# Introduction to Genetics

## Common Terms

- **penetrance**: probability that a gene variant/mutation is observably expressed in an individual that carries it
- **expressivity**: extent of gene expression – refers to the range of variation seen in a phenotype
- **genetic heterogeneity**: a common phenotype/genetic disorder caused by more than one allele or locus mutation
- **phenotypic heterogeneity**: mutations in the same gene resulting in multiple diverse clinical manifestations and degrees of severity
- **mosaicism**: presence of two or more genotypes (e.g. chromosome patterns or gene variants) in the cells of the same person
- **nondisjunction**: an error in cell division where the chromosomes fail to segregate, so both pass to the same daughter cell
- **uniparental disomy**: two full or partial copies of a chromosome from one parental origin and no corresponding full/partial chromosome from the other parent

## Copy Number Variation

- duplication or deletion events that result in variation in the number of genomic sections between individuals. CNVs can be part of normal spectrum of genetic variation
  - decrease: deletion of a chromosomal region, leaving only one copy of the genetic material in that region (e.g. 22q11.2 deletion syndrome due to deletion on one copy of chromosome 22) or leaving no copies in the case of X chromosome material in a male
  - increase: duplication of a chromosomal region, resulting in more than two copies of the genetic material in that region (e.g. Potocki-Lupski syndrome due to duplication of chromosome 17p11.2) or more than one copy in the case of X chromosome material in a male

## Mendelian Inheritance

- traits or disorders determined by a gene at a single locus
- autosomal inheritance: disorder is caused by mutations in genes on one of 22 pairs of autosomes (chromosomes 1-22)
  - autosomal dominant: one copy of a gene with a mutation is enough to cause a trait/disorder
  - autosomal recessive: both copies of a gene must have mutations to cause a trait/disorder; one copy of mutation = carrier
- x-linked inheritance: when disease is caused by mutations in a gene on the X chromosome; generally results in a trait/disorder that is seen more commonly or with greater severity in males than females

## Triplet Repeat Expansions

- disorders where the number of trinucleotide repeats in certain genes exceeds the normal number and result in altered gene expression or production of an abnormal protein
  - these disorders can demonstrate genetic anticipation, where signs and symptoms appear more severe and at an earlier age from each generation to the next
  - length of expansion segment is often proportional to severity of clinical phenotype
- examples: Fragile X syndrome, Huntington disease

## Imprinting Disorders

- imprinted genes are expressed entirely from either the maternal or paternal allele, depending on the gene (parent-of-origin gene expression)
- occur when a mutation disrupts the normally expressed allele of imprinted gene, or through uniparental disomy of the normally silenced allele
- examples: Prader-Willi syndrome, Angelman syndrome, Beckwith-Wiedemann syndrome

## Mitochondrial Disorders

- disorders caused by mutations in mitochondrial DNA or nuclear genes whose protein products are important for mitochondrial function. High phenotypic heterogeneity

- mother passes on the defect to all of her children; father cannot pass on defect since embryo only receives mitochondria from the mother (in the egg)
- examples: mitochondrial enceophalomyopathy and lactic acidosis with stoke-like episodes (MELAS) syndrome, Leigh syndrome, Kearns-Sayre syndrome, myoclonic epilepsy with ragged red fibres (MERRF) syndrome

# Pedigrees

- diagrams of a family tree that show the pattern/distribution of phenotypes for a genetic disorder within that family, often across multiple generations

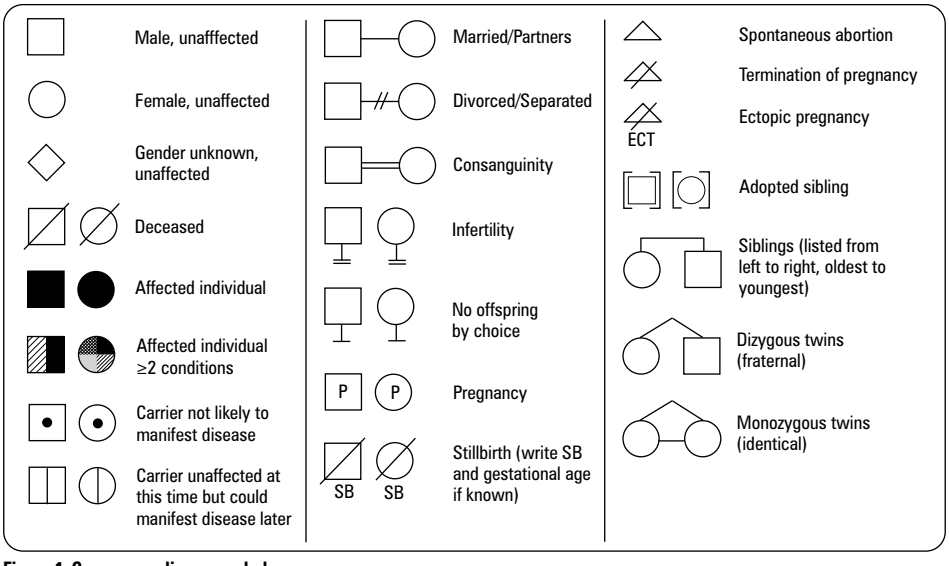



**Figure 1. Common pedigree symbols**

# Genetic Testing and Counselling

## Common Terms

- presymptomatic genetic testing: to determine whether individuals without current symptoms, but with a known family history of a genetic disease, carry the mutation associated with the disease
- linkage studies/indirect DNA studies: studies that look at markers (known DNA sequences) around the gene in question, due to an inability to study the gene itself
- newborn screening: performed within first few days of life to detect treatable, potentially fatal disorders before symptoms arise to allow for early therapy
- preconception genetic counselling: pre-pregnancy examination to assess risk of having a child with an inherited condition

**Table 1. Common Genetic Tests**

| Test | Karyotype | FISH | Microarray Analysis | Sanger Sequencing | NGS/WES |
|---|---|---|---|---|---|
| **Technique** | Microscopic analysis of chromosomes with a special stain that shows large changes in the number or structure of chromosomes; can detect large CNVs | A fluorescent-tagged DNA probe used to identify a gain, loss or rearrangement of chromosomal material | Array comparative genomic hybridization (CGH): a collection of DNA probes attached to a solid surface to which test DNA hybridizes in order to determine copy number of DNA regions | A method of DNA sequencing which is based on the selective incorporation of chain-terminating nucleotides during replication | High-throughput method to sequence multiple genes, or whole exome |
| **Uses/Indications** | Useful to identify major aneuploidies, structural chromosomal rearrangements, chromosomal changes related to hematological conditions, or other genetic diseases related to chromosome structure | Can confirm the presence or absence of specific DNA sequences, and localize them. May be used to detect aneuploidies or balanced rearrangements, in gene mapping or identification of oncogenes, and in identification of circulating tumour cells | Microarray analysis can identify small deletions or duplications of genetic material anywhere in the genome Commonly indicated when there is developmental delay/ autism OR two or more congenital anomalies | The "gold-standard" method for identification of single nucletotide variants in the gene(s) known to cause suspected syndrome | NGS is useful for multi-gene test panels when multiple genes are associated to a given indication. WES is useful when genetic syndrome is suspected, but the diagnosis is unclear |

**Meta-analysis of the Diagnostic and Clinical Utility of Genome and Exome Sequencing and Chromosomal Microarray in Children**
Genomic Med 2018;3:16
**Objective**: To compare the diagnostic and clinical utility of genome and whole-exome sequencing to the chromosomal microarray.
**Methods**: A systematic review and meta-analysis of the literature.
**Results**: 37 studies were included (20, 068 children). Diagnostic utility of whole-genome sequencing (0.41, 95% CI 0.34-0.48) and whole-exome sequencing (0.36, 95% CI 0.33-0.40) were greater than chromosomal microarray (0.10, 95% CI 0.08-0.12). The clinical utility of whole-genome sequencing (0.27, 95% CI 0.17-0.40) and whole-exome sequencing (0.17, 95% 0.12-0.24) were higher than chromosomal microarray (0.06, 95% CI 0.05-0.07) and this difference was significant for whole genome sequencing vs chromosomal microarray ($p<0.0001$).
**Conclusion**: The diagnostic and clinical utility of whole genome and exome sequencing is greater than chromosomal microarray.

**Table 2. Prenatal and Newborn Screening Tests**

| Test | FTS | Enhanced FTS | IPS | NIPT | Fetal Anatomy Scan | Newborn Screening |
|---|---|---|---|---|---|---|
| **Technique/ Indications** | Biochemistry (β-hCG, PAPP-A) US estimate of gestational age and measurement of nuchal translucency | Biochemistry (β-hCG, PAPP-A, AFP, placental growth factor) also uses nuchal translucency measurement and maternal age | Use results from FTS and combine with additional biomarkers (inhibin A, unconjugated estradiol, AFP, 2nd trimester β-hCG) | Uses cell-free DNA from placenta that circulates in maternal blood<br><br>Consider if: advanced maternal age (≥40), abnormal FTS/IPS screen, previous trisomy, NT ≥3.5 mm | Ultrasound | Heel puncture to collect blood, many conditions tested by tandem-mass spectrometry<br><br>Performed on all newborns in Canada with varying conditions screened depending on provinces |
| **Gestational Age (GA)** | 11 and 14 wk GA | 11 and 13 wk GA | 15-21 wk GA | 9-10 wk GA | 18-20 wk GA | After birth |
| **Uses** | Screens for trisomy 21 and 18, sensitivity80-85% | Screens for trisomy 21 and 18, sensitivity 85-90% | Screens for ONTD, trisomy 21 and 18; improved sensitivity, reduced false positive rate compared to FTS (sensitivity for Down's syndrome 85-90%) | Screens for trisomy 21, 13 and 18, and sex chromosome aneuploidies; improved sensitivity and specificity compared to IPS/FTS | Screens for congenital anomalies and soft markers that may suggest a genetic syndrome | Screens for treatable disorders (e.g. CF, congenital hypothyroidism, congenital adrenal hyperplasia, SCID, hemoglobinopathies, metabolic diseases, (e.g. PKU), etc.) |

# Dysmorphisms

## Congenital Anomalies

### Minor and Major Anomalies
- minor anomaly: an unusual anatomic feature that is of no serious medical or cosmetic consequence to the patient
- major anomaly: anomaly that creates significant medical, surgical or cosmetic problems for the patient

### Mechanisms for Anomalies
- malformation: results from an intrinsically abnormal developmental process (e.g. polydactyly)
- disruption: results from the extrinsic breakdown of, or interference with, an originally normal developmental process (e.g. amniotic band disruption sequence)
- deformation: alteration of the final form of a structure by mechanical forces (e.g. Potter deformation sequence)
- dysplasia: abnormal development that results in abnormal organization of cells into tissues (e.g. skeletal dysplasia)

### Multiple Anomalies
- association: non-random occurrence of multiple independent anomalies that appear together more than would be predicted by chance but are not known to have a single etiology (e.g. VACTERL)
- sequence: related anomalies that originate from a single initial major anomaly or precipitating factor that changes the development of other surrounding or related tissues or structures (e.g. Potter sequence or Pierre-Robin sequence)
- syndrome: a pattern of anomalies that occur together and are known or thought to have a single cause (e.g. CHARGE syndrome)



**VACTERL Association**
- **V** **V**ertebral dysgenesis
- **A** **A**nal atresia (imperforate anus) ± fistula
- **C** **C**ardiac anomalies
- **T-E** **T**racheo**E**sophageal fistula ± esophageal atresia
- **R** **R**enal anomalies
- **L** **L**imb anomalies

## Approach to the Dysmorphic Child

- congenital abnormalities are the most common cause of infant death in developed countries

### General Approach to the Dysmorphic Child
- Are the anomalies major or minor?
- What is the mechanism underlying the anomaly?
- Do the anomalies fit as part of an association, sequence, or syndrome?

### History
- prenatal/obstetrical history (see Obstetrics, OB4) with particular attention to potential teratogenic exposures, developmental history (see Pediatrics, P23), and past medical history
- complete three generation family pedigree: health history, consanguinity, multiple miscarriages/ stillbirths, neonatal deaths, congenital defects, intellectual disability/autism, ethnicity

## Physical Exam

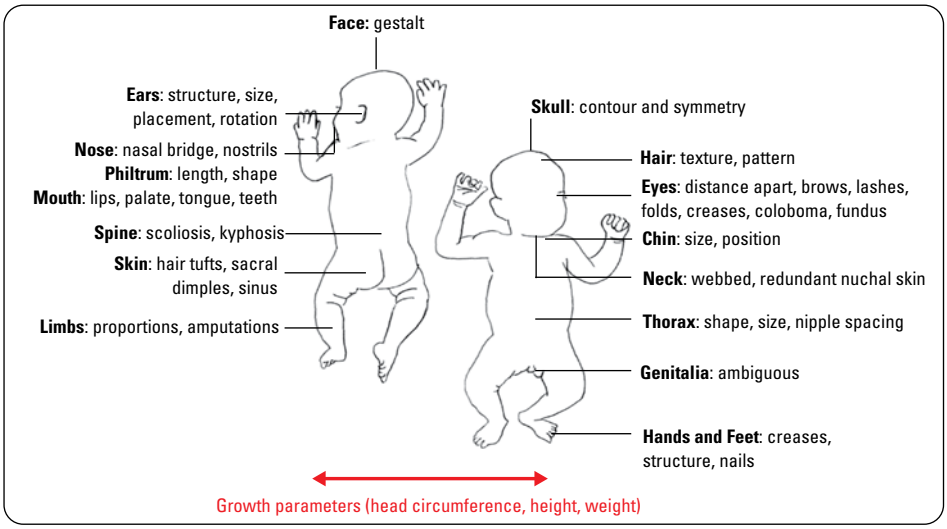



**Figure 2. Physical exam in genetic assessment of a child**

## Investigations

- screening for TORCH infections
- serial photographs if child is older
- x-rays for bony abnormalities
- abdominal ultrasound and echocardiography to rule out structural abnormalities of organs
- cytogenetic studies
  - chromosomal microarray analysis (array CGH) if developmental delay/autism OR two or more congenital anomalies
  - FISH if aneuploidy syndrome (e.g. trisomy 13, 18, or 21) suspected
  - karyotype to consider only if a known aneuploidy syndrome is recognized or if there is a family history of a chromosomal rearrangement such as a translocation
- biochemistry: various biochemical tests, specific enzyme assays (eg. for lysosomal storage diseases)
- single gene testing, multi-gene panel testing, WES

Check the umbilical cord for 2 arteries and 1 vein. The presence of a single umbilical artery may be associated with other congenital anomalies

## Management

- recurrence risk and prenatal counselling
- referral for specialized pediatric or genetic care for symptomatic management
- specific treatments are available for certain metabolic disorders and genetic syndromes
  - metabolic disorders: enzyme replacement therapy, substrate reduction therapy (e.g. low-protein diet in PKU patients)
  - genetic syndromes: e.g. mTOR inhibitors in tuberous sclerosis

# Syndromes and Diseases

### Table 3. Common Chromosomal Aneuploidy Syndromes

| | Trisomy 21 | Trisomy 18 | Trisomy 13 |
|---|---|---|---|
| **Disease** | Down syndrome | Edwards syndrome | Patau syndrome |
| **Incidence** | 1:600-800 births<br>Most common abnormality of autosomal chromosomes<br>Rises with advanced maternal age from 1:1500 at age 20 to 1:20 by age 45 | 1:6000 live births<br>F:M = 3:1 | 1:10,000 live births |
| **Cranium/Brain** | Mild microcephaly, flat occiput, third fontanelle, brachycephaly | Microcephaly, prominent occiput | Microcephaly, sloping forehead, scalp defect, holoprosencephaly |
| **Eyes** | Upslanting palpebral fissures, epicanthal folds, speckled iris (Brushfield spots), refractive errors (myopia), acquired cataracts, nystagmus, strabismus | Microphthalmia, hypotelorism, iris coloboma, retinal anomalies | Microphthalmia, corneal abnormalities |
| **Ears** | Low-set, small, overfolded upper helix, frequent acute otitis media, hearing loss | Low-set, malformed | Low-set, malformed |
| **Facial Features** | Protruding tongue, large cheeks, low flat nasal bridge, small nose | Cleft lip/palate<br>Small mouth, micrognathia | 60-80% cleft lip and palate |
| **Skeletal/MSK** | Short stature<br>Excess nuchal skin<br>Joint hyperflexibility (80%) including dysplastic hips, vertebral anomalies, atlantoaxial instability | Intrauterine growth restriction<br>Clenched fist with overlapping digits, hypoplastic nails, clinodactyly | Small head size<br>Polydactyly |
| **Cardiac Defect** | 50%, particularly atrioventricular septal defect | 60% (ventricular septal defect, patent ductus arteriosus, atrial septal defect) | 80% (ventricular septal defect, patent ductus arteriosus, atrial septal defect) |
| **GI** | Duodenal/esophageal/anal atresia, tracheoesophageal fistula, Hirschsprung's disease, chronic constipation | Hernia, tracheoesophageal fistula | |
| **GU** | Cryptorchidism, rarely fertile | Polycystic kidneys, cryptorchidism | Polycystic kidneys |
| **CNS** | Hypotonia at birth<br>Low IQ, developmental delay, hearing problems<br>Onset of Alzheimer's disease in 40s | Hypertonia | Hypo- or hypertonia<br>Seizures, deafness |
| **Other Features** | Single transverse palmar crease, clinodactyly and absent middle phalanx of the 5th finger<br>1% lifetime risk of leukemia<br>Polycythemia<br>Hypothyroidism | Small for gestational age<br>Rocker-bottom feet | Single umbilical artery<br>Midline anomalies: scalp, holoprocencephaly, palate, heart, umbilicus, anus |
| **Prognosis/ Management** | Long-term management per AAP Guidelines (Health Supervision of Children with Down Syndrome): CBC, Echo, yearly thyroid test, atlanto-occipital x-ray at 2 yr, sleep study, hearing test and ophthalmology assessment | 13% 1 year survival, 10% ten year survival<br>Profound intellectual disability in survivors | 20% 1 year survival, 13% ten year survival<br>Profound intellectual disability in survivors |

### Table 4. Common Genetic Disorders Involving the Sex Chromosomes

| | Fragile X Syndrome | Klinefelter Syndrome | Turner Syndrome |
|---|---|---|---|
| **Genotype** | CGG trinucleotide repeat expansion in *FMR1* gene on X chromosome | 47,XXY (most common)<br>48,XXXY, 49,XXXXY | 45,X (most common) |
| **Incidence** | 1:3600 males, 1:6000 females<br>Most common heritable cause of intellectual disability in boys | 1:1000 live male births<br>Increased risk with advanced maternal age | 1:4000 live female births<br>Risk not increased with advanced maternal age |
| **Phenotype** | Overgrowth: macrocephaly, prominent jaw, forehead, and nasal bridge with long and thin face, large protuberant ears, macroorchidism, hyperextensibility, and high arched palate<br>Complications: seizures, scoliosis, mitral valve prolapse<br>Premutation carriers (males more often than females) may demonstrate tremor/ataxia syndrome in later life | Tall, slim, underweight<br>No features pre-puberty<br>Post-puberty: variable learning/behavioural difficulties, long limbs, gynecomastia, lack of facial hair | Short stature, short webbed neck, low posterior hair line, wide carrying angle<br>Broad chest, widely spaced nipples<br>Lymphedema of hands and/or feet, cystic hygroma in newborn with polyhydramnios, lung hypoplasia<br>Coarctation of aorta, bicuspid aortic valve<br>Renal and cardiovascular abnormalities, increased risk of HTN<br>Less severe spectrum with mosaic |
| **IQ and Behaviour** | Mild to moderate intellectual disability, 20% of affected males have normal IQ<br>ADHD and/or autism<br>Females with full mutation may show milder intellectual impairment | Mild intellectual disability or learning difficulties<br>Behavioural or psychiatric disorders – anxiety, shyness, aggressive and impulsive behaviour acts | Typically normal intelligence |
| **Gonad and Reproductive Function** | Premutation carrier females at risk of developing premature ovarian failure | Infertility due to hypergonadotropic hypogonadism | Streak ovaries with deficient follicles, infertility, primary amenorrhea, impaired development of secondary sexual characteristics |
| **Diagnosis** | Molecular testing of FMR1 gene: PCR and/or Southern blot analysis of trinucleotide repeat length | Karyotype | Karyotype |

**Table 5. Examples of Other Genetic Syndromes**

| | 22q11.2 Deletion Syndrome | Prader-Willi Syndrome | Angelman Syndrome | Noonan Syndrome | CHARGE Syndrome | Marfan Syndrome |
|---|---|---|---|---|---|---|
| **Genotype** | Microdeletions of chromosome region 22q11.2 | Lack of expression of genes on paternal chromosome 15q11-13 due to deletion, maternal uniparental disomy of chromosome 15, or imprinting defect | Lack of expression of genes on maternal chromosome 15q11-13 due to deletion, paternal uniparental disomy of chromosome 15, or an imprinting defect<br>Rarely due to mutations in *UBE3A* | Autosomal dominant with variable expression, mutations in RAS/MPK pathway genes ("RASopathies") | 2/3 of children with CHARGE have been found to have a CHD7 mutation on chromosome 8 | Mutations in FBN1 gene |
| **Incidence** | 1:4000; second most common genetic diagnosis (next to Down syndrome) | 1:15,000 | 1:10,000 | 1:2000 | 1:10,000 | 1:3000-5000 |
| **Clinical Features** | **"CATCH 22"**<br>**C**yanotic CHD<br>**A**nomalies: craniofacial anomalies, micrognathia and low set ears<br>**T**hymic hypoplasia: immunodeficiency<br>**C**ognitive impairment<br>**H**ypoparathyroidism, hypocalcemia<br>**22**q11 microdeletions<br>High risk for schizophrenia and other psych disorders | **"$H_3O$": H**ypotonia and weakness, **H**ypogonadism, obsessive **H**yperphagia, **O**besity<br>Short stature, almond-shaped eyes, small hands and feet with tapering of fingers<br>Developmental delay (variable)<br>Hypopigmentation, type 2 DM | Ataxia with severe intellectual disability, seizures, tremulousness, midface hypoplasia, large mouth, fair hair, inappropriately happy demeanour/laughter | Short stature, webbed neck, hypertelorism, low set ears, epicanthal folds, ptosis, pectus excavatum<br>Right-sided CHD, pulmonary stenosis<br>Increased risk of hematological cancers, cardiomyopathy, moderate intellectual disability, delayed puberty | **"CHARGE"**<br>**C** **C**oloboma<br>**H** congenital **H**eart disease<br>**A** choanal **A**tresia<br>**R** mental **R**etardation<br>**G** **G**U anomalies<br>**E** **E**ar anomalies | Tall and slender build, disproportionately long limbs and digits, aortic dilatation, lens detachment, pneumothoraces |

**Table 6. Examples of Familial Cancer Syndromes**

| Syndrome | Gene | Associated Cancers | Screening and Monitoring |
|---|---|---|---|
| **Li-Fraumeni Syndrome** | *TP53* | Breast, osteosarcoma, leukemia, soft tissue carcinoma, and numerous other cancers | **Women:**<br>Age 20-29: annual breast MRI<br>Age 30-75: annual breast MRI and mammogram<br>**Men and Women:**<br>Age 18: annual dermatologic examination<br>Age 25: colonoscopy and upper endoscopy every 2-5 yr<br>*(Moderate recommendation)* |
| **Lynch Syndrome (HNPCC)** | *MSH2, MLH1, MSH6, PMS2, EPCAM* | Colorectal, endometrial, ovarian, renal, pancreatic, liver/biliary duct, stomach, brain, breast | Age 20-25 (or 2-5 yr younger than CRC in family): colonoscopy every 1-2 yr<br>Age 30 yr (MSH6) and 35 (PMS2): colonoscopy every 1-2 yr<br>*(Strong recommendation)* |
| **Familial Adenomatous Polyposis (FAP)** | *APC* | Colorectal, small intestine/stomach tumours | Age 10: sigmoidoscopy or colonoscopy every 1-2 yr, colonoscopy once polyps develop<br>*(Strong recommendation)* |
| **Hereditary Breast and Ovarian Cancer Syndrome** | *BRCA1, BRCA2* | Female: breast, ovarian, pancreatic<br>Male: prostate, breast, pancreatic | Age 25-65: annual breast MRI<br>Age 30: annual breast MRI and mammograms<br>*(Strong recommendation)* |
| **Von Hippel-Lindau Syndrome** | *VHL* | Kidney + tumours (e.g. pheochromocytoma) | Age 2: annual physical examination, annual ophthalmologic examination, consider annual catecholamine assessment<br>Consider baseline audiometry at age of school entry<br>Ages 12, 15, and 18: MRI of brain stem, spine, and abdomen, with abdominal ultrasound in alternating years<br>Age 20: MRI every 2 yr<br>*(Expert opinion)* |
| **Cowden Syndrome** | *PTEN* | Breast, thyroid, endometrial | **Women:**<br>Age 30 (or 5-10 yr before earliest breast cancer in the family): annual mammography<br>Age 30: consider random annual endometrial biopsy and/or ultrasound<br>**Men and Women:**<br>At diagnosis: annual thyroid ultrasound<br>Children: evaluation for neurodevelopmental disorders<br>Age 18: annual comprehensive physical exam<br>Age 30-35: colonoscopy every 5 yr<br>*(Moderate recommendation)* |
| **Neurofibromatosis (NF)** | | | |
| Type 1 | *NF1* | Astrocytoma, optic glioma, neurofibroma, leukemia | **Children**: evaluation for neurodevelopmental disorders<br>Annual physical exam including evaluation of growth, blood pressure, skin examination, bone examination, neurological examination, and vision screening<br>*(Expert opinion)* |
| Type 2 | *NF2* | Vestibular schwannoma, meningioma, ependymoma, astrocytoma | Annual physical exam including audiology assessment<br>Age 10: annual brain MRI, spinal MRI every 2-3 yr<br>*(Expert opinion)* |

# Other Single Gene Disorders

## CYSTIC FIBROSIS

- autosomal recessive disease caused by mutation of the CFTR gene which predominantly affects the lungs, but also the gastrointestinal tract
- see Respirology, R12 and Pediatrics, P82

## SICKLE CELL DISEASE

- autosomal recessive disease caused by mutation of the HBB gene resulting in the production of an abnormal version of beta-globin and subsequently distorted red blood cells
- see Hematology, H20

## DUCHENNE MUSCULAR DYSTROPHY

### Epidemiology

- 1:4000 males

### Etiology

- one type of muscular dystrophy characterized by progressive skeletal and cardiac muscle degeneration
- X-linked recessive: 1/3 spontaneous mutations, 2/3 inherited mutations
- missing structural protein (dystrophin) → muscle fibre fragility → fibre breakdown → necrosis and degeneration

### Clinical Feature

- proximal muscle weakness by age 3, positive Gower's sign, waddling gait, toe walking
- pseudohypertrophy of calf muscles (muscle replaced by fat) and wasting of thigh muscles
- decreased reflexes
- non-progressive delayed motor and cognitive development (dysfunctional dystrophin in brain)
- cardiomyopathy



**Gower's Sign**
Child uses hands to "climb up" the legs to move from a sitting to a standing position

### Diagnosis

- molecular genetic studies of dystrophin gene (DMD) (first line)
- family history (pedigree analysis)
- increased CK (50-100x normal) and lactate dehydrogenase
- elevated transaminases
- muscle biopsy, EMG

### Management

- supportive (e.g. physiotherapy, wheelchairs, braces); prevent obesity
- cardiac health monitoring and early intervention
- bone health monitoring and intervention (vitamin D, bisphosphonates)
- steroids (e.g. prednisone or deflazacort)
- surgical (for scoliosis)
- gene therapy trials underway

### Complications

- patient usually wheelchair-bound by age 12
- early flexion contractures, scoliosis, osteopenia of immobility, increased risk of fracture
- death due to pneumonia/respiratory failure or congestive heart failure in second-third decade

# Metabolic Diseases

- individually rare but collectively occur in 1:1500 births
- inherited disorders of metabolism; most are autosomal recessive
- infants and older children may present with failure to thrive or developmental delay
- organelle disorders can present with dysmorphism
- universal newborn screening in Ontario includes some treatable metabolic disorders

Metabolic disease must be ruled out in any newborn who becomes acutely ill after a period of normal behaviour and development, or with a family history of early infant death even if the newborn screen is negative

**Table 7. Metabolic Disorders**

| | Organic and Amino Acid Disorders | Carbohydrate Disorders | Fatty Acid Disorders | Organelle Disorders |
|---|---|---|---|---|
| **Examples of Conditions** | PKU<br>Tyrosinemia<br>Homocystinuria<br>MSUD<br>Alkaptonuria<br>Urea cycle defects | Galactosemia<br>Glycogen storage diseases: von Gierke's, Pompe's, Cori's, Andersen, McArdle | MCAD deficiency<br>VLCAD deficiency<br>LCHAD deficiency | Congenital disorders of glycosylation<br>Lysosomal storage diseases: Hunter's, Hurler's, Niemann-Pick, Tay-Sachs, Gaucher, Fabry, Krabbe<br>Peroxisomal defects: Zellweger syndrome, X linked adrenoleukodystropnhy |
| **Clinical Manifestations** | Coma, Irritability, lethargy, poor feeding<br>Seizures<br>Intellectual disability<br>Vomiting and acidosis after feeding initiation<br>Sweet-smelling urine (MSUD) | Hypoglycemia, Hepatomegaly, liver failure, cardiomyopathy<br>Growth retardation, failure to thrive | Lethargy, poor feeding<br>Seizures, coma<br>Symptoms triggered by fasting<br>Liver dysfunction<br>Sudden infant death | Progressive neurological problems<br>Developmental regression<br>Chronic encephalopathy<br>Developmental delay<br>Bone crises (Gaucher)<br>Deafness, blindness |
| **Laboratory Findings** | Hyperammonemia with normal anion gap (urea cycle defects), hyperammonemia with high anion gap (organic acidemia) | Elevated liver enzymes (Galactosemia)<br>Hypoglycemia, lactic acidosis, hyperlipidemia (GSD) | Hypoketotic hypoglycemia<br>Elevated free fatty acids<br>Elevated creatine phosphokinase | Elevated urine oligosaccharides, (oligosaccharidoses) and glycosaminoglycans (mucopolysaccharidoses), abnormal transferrin isoelectric focusing (congenital disorders of glycosylation), abnormal very long chain fatty acids (peroxisomal defects) |
| **Physical Exam** | Hypotonia/hypertonia<br>Microcephaly, musty odour, eczema, hypopigmentation (PKU)<br>Dark urine, pigmented sclerae, arthralgias (alkaptonuria)<br>Lens subluxation, marfanoid appearance (homocystinuria) | Infantile cataracts (galactosemia)<br>Hepatomegaly<br>Muscle weakness/ cramping | Hepatomegaly<br>Hypotonia | Dysmorphic facial features<br>Macrocephaly (Lysosomal storage diseases)<br>Hepatosplenomegaly (Niemann-Pick type A/B/C, not Tay-Sachs)<br>Cherry-red spot on macula (Niemann-Pick type A/B, Tay-Sachs, Gaucher)<br>Corneal clouding (Hurler)<br>Infantile cataract (Fabry)<br>Peripheral neuropathy (Fabry, Krabbe)<br>Spasticity |

## Initial Investigations for a Child with Acute Problems thought to be Due to an Inborn Error of Metabolism

- important to send lab studies at initial presentation in order to facilitate immediate diagnosis and treatment
- check newborn screening results
- electrolytes, ABGs (calculate anion gap, rule out acidosis)
- CBC with differential and smear
- blood glucose (hypoglycemia seen with organic acidemia, fatty acid oxidation defects, and GSDs)
- lactate, ammonium (hyperammonemia with urea cycle defects or organic acidemias), plasma $Ca^{2+}$ and $Mg^{2+}$, plasma amino acid screen
- routine urinalysis: ketonuria must be investigated, urinary organic acids
- carnitine levels with acylcarnitine profile
- others: urate, urine nitroprusside, cerebrospinal fluid glycine, free fatty acids (3-β-hydroxybutyrate ratio >4 in fatty acid oxidation defect)

## Treatment

- varies according to inborn error of metabolism but includes dietary restrictions, enzyme replacement etc.
- in the presentation of acute decompensation potentially caused by an inborn error of metabolism, discontinue feeding to prevent further build up of toxic metabolites

**Table 8. Presentation and Management of Select Metabolic Disorders**

| | Phenylketonuria | Galactosemia | Maple Syrup Urine Disease | Glycogen Storage Disease Type 1 (Von Gierke Disease) |
|---|---|---|---|---|
| **Epidemiology** | 1:10,000; autosomal recessive disease (mutations in PAH) | 1:60,000; autosomal recessive disease | 1:185,000; autosomal recessive disease (mutations in BCKDHA, BCKDHB, and DBT genes), 1:25,000 Ashkenazi Jewish, 1:400 Mennonites | 1:100,000; autosomal recessive disease, 1:20,000 in Ashkenazi Jewish |
| **Etiology** | Deficiency of phenylalanine hydroxylase prevents conversion of phenylalanine to tyrosine leading to build-up of phenylalanine and its toxic metabolites<br>Mothers who have PKU may have infants with multiple congenital abnormalities | Most commonly due to deficiency of galactose-1-phosphate uridyltransferase leading to an inability to process lactose/galactose | Reduction or elimination of protein complex needed for amino acid leucine, isoleucine, and valine breakdown, leading to toxic build-up | Mutations in G6PC (cause of GSD1a) and SLC37A4 (cause of GSD1b) prevent effective conversion of glucose-6-phosphate to glucose. Glucose-6-phosphate is converted to glycogen and fat which subsequently accumulates in cells, especially in the liver and kidneys |
| **Clinical Feature** | Baby is normal at birth, then develops a musty odour, eczema, hypertonia, tremors and mental retardation<br>Hypopigmentation due to low tyrosine levels (fair hair, blue eyes) | Signs of liver and renal failure, jaundice, failure to thrive, and cataracts with ingestion of lactose/galactose<br><br>Complications:<br>Increased risk of sepsis, especially *E. coli*<br>If the diagnosis is not made at birth, liver and brain damage may become irreversible | Feeding intolerance, failure to thrive, vomiting, lethargy, and maple syrup odour in urine and cerumen<br><br>May progress to irreversible mental retardation, hyperactivity, severe failure to thrive, seizures, coma, cerebral edema, and death if inadequately treated | Typically presents between 3-6 mo of age with hepatomegaly, hypoglycemia, poor fasting tolerance, growth failure and "doll-like" facies (full cheeks with thin extremities)<br><br>Complications:<br>Lactic acidosis, hyperuricemia, hyperlipidemia, delayed puberty, renal disease, hypoglycemic seizures, hepatic adenomas, ostoeporosis |
| **Diagnosis and Management** | PKU screening at birth<br>Dietary restriction of phenylalanine starting within the first 10 d of life; especially important during pregnancy to maintain normal phenylalanine levels to prevent maternal PKU effects on fetus<br>Large neutral amino acid (tyrosine) replacement, BH4 enzyme treatment, phenylalanine lyase treatment are other options | Screened for in many newborn screening programs<br>Elimination of galactose from the diet (e.g. dairy, breast milk)<br>Most infants are fed a soy-based diet | MSUD is screened in most newborn screening programs.<br>Serum amino acid evaluation (leucine, isoleucine, alloleucine, valine) and urine organic acid analysis<br>Protein-restricted, high-carbohydrate diet to limit branched amino acid intake<br>A trial of thiamine therapy in addition may be recommended for some infants | Evaluate hypoglycemia, lactic acidemia, hypertriglyceridemia and hepatomegaly<br><br>Treat with nutrition therapy (small frequent feedings, avoid fructose/sucrose/galactose), continuous overnight feedings, raw cornstarch (for slow, sustained glucose release), vitamin supplementation, frequent blood glucose monitoring |

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# MI Medical Imaging

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# Acronyms

| | |
|---|---|
| $^{18}$FDG | 18-fluorodeoxyglucose |
| AP | anteroposterior |
| ARDS | acute respiratory distress syndrome |
| AV | arteriovenous |
| AXR | abdominal x-ray |
| BOOP | bronchiolitis obliterans organizing pneumonia |
| CHF | congestive heart failure |
| CNS | central nervous system |
| CSF | cerebrospinal fluid |
| CT | computed tomography |
| CTA | computed tomographic angiogram |
| CVD | collagen vascular disease |
| CVP | central venous pressure |
| CXR | chest x-ray |
| DDH | Developmental dysplasia of the hip |
| DEXA | dual-energy x-ray absorptiometry |
| DMSA | dimercaptosuccinic acid |
| DSA | digital subtraction angiography |
| DTPA | diethylene triamine pentaacetic acid |
| DWI | diffusion-weighted image |
| ECD | ethyl cysteinate dimer |
| eGFR | estimated glomerular filtration rate |
| ERCP | endoscopic retrograde cholangio-pancreatography |
| FLAIR | fluid-attenuated inversion recovery |
| GI | gastrointestinal |
| GPA | granulomatosis with polyangiitis |
| GU | genitourinary |
| HCC | hepatocellular carcinoma |
| HIDA | hepatobiliary iminodiacetic acid |
| HMPAO | hexamethylpropyleneamine oxime |
| HSG | hysterosalpingogram |
| IBD | inflammatory bowel disease |
| ICS | intercostal space |
| ICV | ileocecal valve |
| IPF | interstitial pulmonary fibrosis |
| IVP | intravenous pyelogram |
| KUB | kidneys, ureters, bladder |
| LA | left atrium |
| LV | left ventricle |
| MAA | macroaggregated albumin |
| MAG3 | mertiatide |
| MCA | middle cerebral artery |
| MR | magnetic resonance |
| MRA | magnetic resonance angiogram |
| MRCP | magnetic resonance cholangiopancreatography |
| MRI | magnetic resonance imaging |
| MS | multiple sclerosis |
| MUGA | multiple gated acquisition |
| PA | posteroanterior |
| PBD | percutaneous biliary drainage |
| PET | positron emission tomography |
| PFT | pulmonary function test |
| PICC | peripherally-inserted central catheter |
| POCUS | point-of-care ultrasound |
| PTA | percutaneous transluminal angioplasty |
| PTC | percutaneous transhepatic cholangiography |
| RA | right atrium |
| RAIU | radioactive iodine uptake |
| RV | right ventricle |
| SPECT | single photon emission computed tomography |
| SVC | superior vena cava |
| TB | tuberculosis |
| TNK | tenecteplase |
| tPA | tissue plasminogen activator |
| TRUS | transrectal ultrasound |
| TVUS | transvaginal ultrasound |
| U/S | ultrasound |
| VCUG | voiding cystourethrogram |
| V/Q | ventilation/perfusion |

# Imaging Modalities

## X-Ray Imaging

- x-rays are a form of electromagnetic energy of short wavelength
- as x-ray photons traverse matter, they can be absorbed (a process known as "attenuation") and/or scattered
- the density of a structure determines its ability to attenuate or "weaken" the x-ray beam
  - air < fat < water < bone < metal
- structures that have high attenuation (e.g. bone) appear white on the resulting images

### Plain Films

- x-rays pass through the patient and interact with a detection device (film) to produce a 2-dimensional projection image
- structures closer to the film appear sharper and less magnified
- contraindications: pregnancy (relative)
- advantages: inexpensive, non-invasive, readily available, portable, reproducible, fast, easily read
- disadvantages: radiation exposure (minimal), generally poor at distinguishing soft tissues

### Fluoroscopy

- continuous x-rays used for guiding angiographic and interventional procedures, in contrast examinations of the GI tract, and in the OR for certain surgical procedures (e.g. orthopedic, urological)
- on the fluoroscopic image, black and white are reversed so that bone and contrast agents appear dark and radiolucent structures appear bright
- advantages: real-time visualization of structures
- disadvantages: increased radiation dose; however, the use of pulsed fluoroscopy reduces fluoroscopy time by 76% and radiation dose by 64% as compared with continuous fluoroscopy

### Computed Tomography

- x-ray beam opposite a detector moves in a continuous 360° arc as patient is advanced through the scanner
  - anatomical structures are then reconstructed
- attenuation is quantified in Hounsfield units:
  - windowing and leveling: adjusting the "window width" (range of Hounsfield units displayed) and "window level" (midpoint value of the window width) to maximally visualize certain anatomical structures (e.g. CT chest can be viewed using "lung", "soft tissue", and "bone" settings)
- contraindications: pregnancy (relative), adverse reactions to contrast agents (e.g. allergy, renal failure)
- advantages: delineates soft tissues, excellent at delineating bones and identifying lung/liver masses, may be used to guide biopsies, spiral/helical multidetector CT has fast data acquisition and allows 3D reconstruction, CTA non invasive compared to conventional angiography
- disadvantages: high radiation exposure, soft tissue characterization is not as good in comparison with MRI, IV contrast injection, anxiety of patient when going through scanner, higher cost, less available than plain film, typically requires expertise/radiologist interpretation

**Typical Effective Doses from Diagnostic Medical Exposures (in adults)***

| Diagnostic Procedure Type | Equivalent Number of Chest X-Rays | Approximate Equivalent Period of Natural Background Radiation** (~3 mSv/yr) |
|---|---|---|
| **X-Ray** | | |
| Skull | 5 | 12 d |
| Cervical spine | 10 | 3 wk |
| Thoracic spine | 50 | 4 mo |
| Lumbar spine | 75 | 6 mo |
| Chest (single PA film) | 1 | 2 d |
| Shoulder | 0.5 | 1 d |
| Mammography | 20 | 7 wk |
| Abdomen | 35 | 3 mo |
| Hip | 35 | 3 mo |
| Pelvis | 30 | 10 wk |
| Knee | 0.25 | <1 d |
| IVU | 150 | 1 yr |
| Dual-energy x-ray absorptiometry (without/with CT) | 0.5/2 | <1 d/4 d |
| Upper GI series | 300 | 2 yr |
| Small bowel series | 250 | 20 mo |
| Barium enema | 400 | 2.7 yr |
| **CT** | | |
| Head | 100 | 8 mo |
| Neck | 150 | 1 yr |
| Spine | 300 | 2 yr |
| Chest | 350 | 2.3 yr |
| Chest (pulmonary embolism) | 750 | 5 yr |
| Coronary angiography | 800 | 5.3 yr |
| Abdomen | 400 | 2.7 yr |
| Pelvis | 300 | 2 yr |
| **Radionuclide** | | |
| Brain (18FDG) | 705 | 4.7 yr |
| Bone ($^{99m}$Tc) | 315 | 2.1 yr |
| Thyroid ($^{99m}$Tc) | 240 | 1.6 yr |
| Thyroid (123I) | 95 | 8 mo |
| Cardiac rest-stress test ($^{99m}$Tc 1-d) | 470 | 3 yr |
| ($^{99m}$Tc 2-d) | 640 | 4 yr |
| Lung ventilation (133Xe) | 25 | 2 mo |
| Lung perfusion ($^{99m}$Tc) | 100 | 8 mo |
| Renal ($^{99m}$Tc) | 90-165 | 7-13 mo |
| Liver-spleen ($^{99m}$Tc) | 105 | 8.4 yr |
| Biliary tract ($^{99m}$Tc) | 155 | 1 yr |

*Source: *Radiology* 2008;248:254-263
**Calculated using average natural background exposure in Canada (Health Canada: http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/environ/expos-eng.php)

# Ultrasound

- high-frequency sound waves are transmitted from a transducer and passed through tissues; reflections of the sound waves are picked up by the transducer and transformed into images
- reflection (or "echo") occurs when the sound waves reflect off tissue interfaces of different acoustic densities
- structures are described based on their echogenicity; hyperechoic structures appear bright (U/S reflected) whereas hypoechoic structures appear dark (U/S waves not reflected back but pass through)
- a gel is used on the skin surface for impendence matching between the skin and transducer
- higher U/S frequencies result in greater resolution, however, deeper structures are more difficult to visualize due to weaker penetration
- artifacts: acoustic shadowing refers to the echo-free area located behind an interface that strongly reflects (e.g. air) or absorbs (e.g. bone) sound waves; enhancement refers to the increase in reflection amplitude (i.e. increased brightness) from objects that lie below a weakly attenuating structure (e.g. cyst)
- Duplex scan: grey-scale imaging that utilizes the Doppler effect (sound reflecting off a moving target) to visualize the velocity of blood moving past the transducer
- Colour Doppler: assigns a colour based on the direction of blood flow (i.e. red = toward transducer, blue = away)
- advantages: relatively low cost, non-invasive, no radiation, portable, real-time imaging, may be used for guided biopsies, many different imaging planes (axial, sagittal), differentiates cystic vs. solid
- disadvantages: highly operator-dependent, air in bowel may prevent imaging of midline structures in the abdomen, may be limited by patient habitus, poor for bone evaluation, low field-of-view



**Attenuation**
Bone (= bright) > grey matter > white matter ("fatty" myelin) > CSF > air (= dark)

# Magnetic Resonance Imaging

- imaging technique that does not use ionizing radiation and can produce images in virtually any plane
- patient is placed in a magnetic field generated by electric current; protons. typically from water molecules, align themselves along the plane of magnetization due to their intrinsic polarity. A pulsed radiofrequency beam is subsequently turned on and deflects all the protons off their aligned axes. When the radiofrequency beam is turned off, the protons return to their pre-excitation axis, giving off the energy they absorbed. This energy is measured with a detector and interpreted by software to generate MR images
- the MR image reflects the signal intensity picked up by the receiver. This signal intensity is dependent on:
  1. hydrogen density: tissues with low hydrogen density (e.g. cortical bone, lung) generate little to no MR signal compared to tissues with high hydrogen density (e.g. water)
  2. magnetic relaxation times (T1 and T2): reflect quantitative alterations in MR signal strength due to intrinsic properties of the tissue and its surrounding chemical and physical environment



Remember that water is "**w**hite" on **T2** as "**W**orld **W**ar **II**"



**Methods to Reduce the Risk of Contrast-Induced Nephropathy**
- Optimal: 0.9% NaCl at 1 ml/kg/h for 12 h pre-procedure and 12 h post-contrast administration
- For same-day procedure: 0.9% NaCl or $NaHCO_3$ at 3 ml/kg/h for 1-3 h pre-procedure and for 6 h post-contrast administration

**Table 1. Differences Between Diffusion, T1- and T2-Weighted MR Imaging**

| Imaging Techniques | Contrast Enhancements | Main Application | Advantages |
|---|---|---|---|
| **Diffusion-Weighted Imaging** | Contrast dependent on the molecular motion of water<br>Decreased diffusion is hyperintense (bright), whereas increased diffusion is hypointense (dark) | Neuroradiology | Sensitive for detection of acute ischemic stroke and differentiating an acute stroke from other neurologic pathologies<br>Acute infarction and abscess collections appear hyperintense due to restricted diffusion |
| **T1-Weighted** | Fluid is hypointense (dark) and fat is hyperintense (bright) | Body soft tissues | Often considered an anatomic scan since they provide a reference for functional imaging |
| **T2-Weighted** | Fluid is hyperintense (bright) and fat is hypointense (dark) | Body soft tissues | Often considered a pathologic scan since they will highlight edematous areas associated with certain pathologies |

# Positron Emission Tomography Scans

- nuclear tracers are employed to prodce images of functional processes in the body
- current generation models integrate PET and CT technologies into a single imaging device (PET-CT) that collects both anatomic and functional information during a single acquisition
- positron-producing radioisotopes, such as 18F, are chemically incorporated into a metabolically active molecule (e.g. glucose). These are then injected into the patient, where they travel to and accumulate in the tissues of interest. As the radioactive substance decays, γ rays are produced, and are detected by the PET scanner
- contraindications: pregnancy
- advantages: shows metabolism and physiology of tissues (not only anatomic); in oncology, allows for diagnosis, staging, and restaging; has predictive and prognostic value; can evaluate cardiac viability
- disadvantages: cost, ionizing radiation, availability



**Contraindications to IV Contrast**

**MADD Failure**
**M**ultiple myeloma
**A**dverse reaction previously
**DM**
**D**ehydration
**F**ailure (renal, severe heart)

# Contrast Enhancement

**Table 2. Contrast Agents**

| Imaging Modality | Types | Advantages | Disadvantages | Contraindications |
|---|---|---|---|---|
| **X-Ray/CT** | 1. Barium (oral or rectal) | Radio-opaque substance that helps to delineate intraluminal anatomy; may demonstrate patency, lumen integrity, or large filling defects | | Previous adverse reaction to contrast; barium enema is contraindicated in toxic megacolon, acute colitis, and suspected perforation |
| | 2. Iodine (IV injection) | Delineates intraluminal anatomy; may demonstrate patency, lumen integrity, or large filling defects; under fluoroscopy, may also give information on function of an organ | | Previous adverse reaction to contrast, renal failure, DM, pregnancy, multiple myeloma, severe heart failure and dehydration eGFR <60 may require preventative measures and follow-up |
| **MRI** | Gadolinium-Chelates (IV injection) | Shortens T1 relaxation time, thereby increasing signal intensity in T1-weighted sequences; gadolinium has some effect on T2-relaxation time; highlights highly vascular structures (e.g. tumours) | Risk of nephrogenic systemic fibrosis in patients with end-stage renal disease | Previous adverse reaction to contrast or end-stage renal disease (relative contraindication) |
| **U/S** | Microbubbles (IV injection) | Since gas is highly echogenic, the microbubbles allow for echo-enhancement of a tissue | | Contraindicated in individuals with right-to-left cardiac shunts or people with known hypersensitivity reactions |

# Chest Imaging

## Chest X-Ray

### Standard Views

- PA: anterior chest against film plate to minimize magnification of the heart size
- lateral: better visualization of retrocardiac space and thoracic spine (more sensitive at picking up pleural effusions)
  - helps localize lesions when combined with PA view
- AP: for bedridden patients (generally a lower quality film than PA because of enlarged cardiac silhouette)
- lateral decubitus: to assess for pleural effusion and pneumothorax in bedridden patients; however, point of care ultrasound (POCUS) can also be utilized for both of these purposes
- lordotic: angled beam allowing better visualization of apices normally obscured by the clavicles and anterior ribs

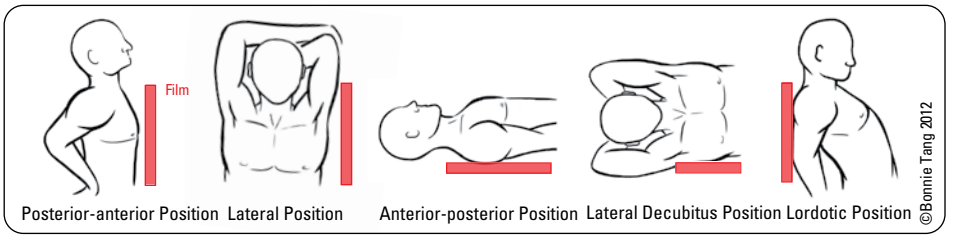



**Figure 1. CXR views**

### Approach to CXR

### Basics

- ID: patient name, MRN, sex, age
- date of exam
- markers: right and/or left
- technique: view (e.g. PA, AP, lateral), supine or erect
- indications for the study
- comparison: date of previous study for comparison (if available)
- quality of film: inspiration (6th anterior and 10th posterior ribs should be visible), penetration (thoracic spine should be visible) and rotation (clavicles vs. spinous process)

## Analysis

- tubes and lines: check position and be alert for pneumothorax or pneumomediastinum
- soft tissues: neck, axillae, pectoral muscles, breasts/nipples, chest wall
  - nipple markers can help identify nipples (may mimic lung nodules)
  - amount of soft tissue, presence of masses and air (subcutaneous emphysema)
- abdomen (see *Abdominal Imaging*, MI10)
  - free air under the diaphragm, air-fluid levels, distention in small and large bowel
  - herniation of abdominal contents (i.e. diaphragmatic hernia)
- bones: C-spine, thoracic spine, shoulders, ribs, sternum, clavicles
  - lytic and blastic lesions and fractures
- mediastinum: trachea, heart, great vessels
  - cardiomegaly (cardiothoracic ratio >0.5), tracheal shift, tortuous aorta, widened mediastinum
- hila: pulmonary vessels, mainstem and segmental bronchi, lymph nodes
- lungs: parenchyma, pleura, diaphragm
  - comment on abnormal lung opacity, pleural effusions or thickening
  - right hemidiaphragm usually higher than left due to liver
  - right vs. left hemidiaphragm can be discerned on lateral CXR due to heart resting directly on left hemidiaphragm
- please refer to Toronto Notes website for supplementary material on how to approach a CXR

**Chest X-Ray Interpretation**

**Basics ABCDEF**
**A**P, **P**A or other view
**B**ody position/rotation
**C**onfirm name
**D**ate
**E**xposure/quality
**F**ilms for comparison

**Analysis ABCDEF**
**A**irways and hilar **A**denopathy
**B**ones and **B**reast shadows
**C**ardiac silhouette and **C**ostophrenic angle
**D**iaphragm and **D**igestive tract
**E**dges of pleura
**F**ields (lung fields)

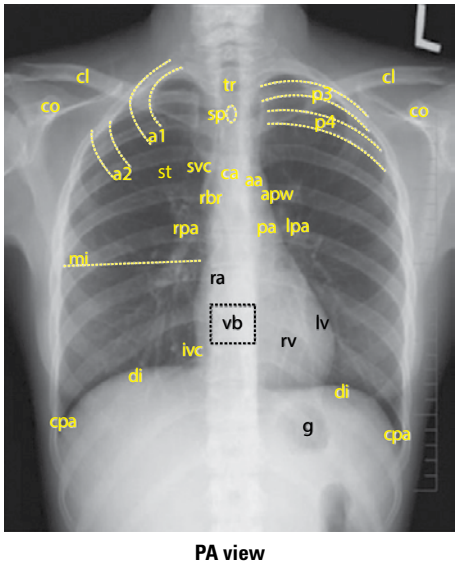
## Anatomy

## Localizing Lesions for Parenchymal Lung Disease

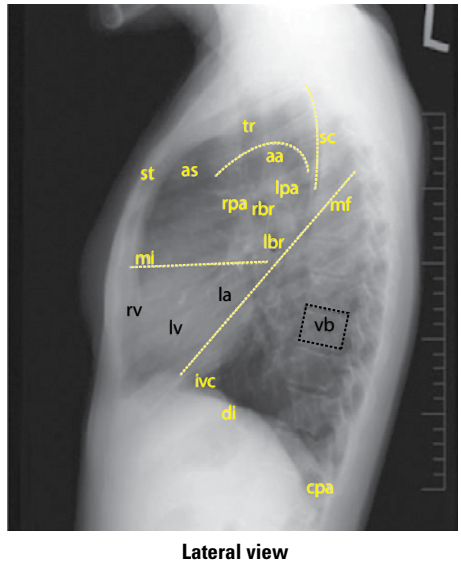
- silhouette sign: when two objects of the same radiolucency contact each other, they become indistinguishable on imaging and result in the loss of normal interfaces (i.e. the silhouette expected at an anatomical border disappears). The silhouette sign can be used to identify lung pathology (consolidation, atelectasis, mass) and localize disease to specific lung segments. This sign is not only used in the chest, but can also be an aid to interpreting imaging studies throughout the body
- spine sign: on lateral films, vertebral bodies should appear progressively radiolucent (dark) as one moves down the thoracic vertebral column; if they appear more radio-opaque, it is an indication of pathology (e.g. consolidation in overlying lower lobe)
- air bronchogram: branching pattern of air-filled bronchi on a background of opacification/fluid-filled airspaces

**Table 3. Localization Using the Silhouette Sign**

| Interface Lost | Location of Lung Pathology |
|---|---|
| SVC/right superior mediastinum | RUL |
| Right heart border | RML |
| Right hemidiaphragm | RLL |
| Aortic knob/left superior mediastinum | LUL |
| Left heart border | Lingula |
| Left hemidiaphragm | LLL |




PA view

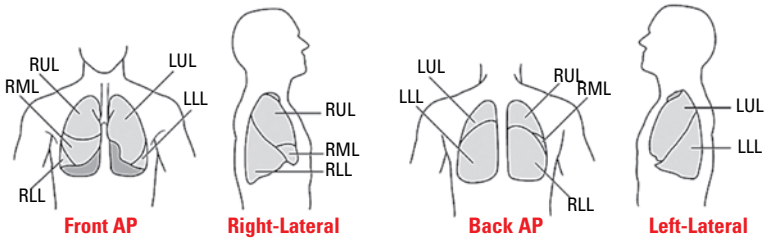



Lateral view

**Legend**

| | |
|---|---|
| a1 | anterior 1st rib |
| a2 | anterior 2nd rib |
| aa | aortic arch |
| apw | aorto-pulmonary window |
| as | anterior airspace |
| ca | carina |
| cl | clavicle |
| co | coracoid process |
| cpa | costophrenic angle |
| di | diaphragm |
| g | gastric bubble |
| ivc | inferior vena cava |
| la | left atrium |
| lbr | left mainstem bronchus |
| lpa | left pulmonary artery |
| lv | left ventricle |
| mf | major fissure |
| mi | minor fissure |
| p3 | posterior 3rd rib |
| p4 | posterior 4th rib |
| pa | main pulmonary artery |
| ra | right atrium |
| rbr | right mainstem bronchus |
| rpa | right pulmonary artery |
| rv | right ventricle |
| sc | scapula |
| sp | spinous process |
| st | sternum |
| svc | superior vena cava |
| tr | trachea |
| vb | vertebral body |

**Figure 2. Location of fissures, mediastinal structures, and bony landmarks on CXR**




RUL: Right Upper Lobe; RML: Right Middle Lobe; RLL: Right Lower Lobe; LUL: Left Upper Lobe; LLL: Left Lower Lobe

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**Figure 3. Location of lobes of the lung**

# Computed Tomography Chest

## Approach to CT Chest

- soft tissue window
  - thyroid, chest wall, pleura
  - heart: chambers, coronary artery calcifications, pericardium
  - vessels: aorta, pulmonary artery, smaller vasculature
  - lymph nodes: mediastinal, axillary
- bone window
  - vertebrae, sternum, ribs: fractures, lytic lesions, sclerosis
- lung window
  - trachea: patency, secretions
  - bronchi: anatomic variants, mucus plugs, airway collapse
  - lung parenchyma:, nodules, fibrosis,interstitial changes,consolidation
  - pleural space: effusions
- please refer to Toronto Notes website for supplementary material on how to approach a CT chest

**Table 4. Types of CT Chest**

| | Advantage | Disadvantage | Contrast | Indication |
|---|---|---|---|---|
| **Standard** | Scans full lung very quickly (<1 min)<br>± high resolution reconstructions | Radiation | ± | CXR abnormality<br>Pleural and mediastinal abnormality<br>Lung cancer staging<br>Cancer follow-up<br>Empyema vs. abscess |
| **Low Dose** | 1/5th the radiation | Decreased detail | No | Lung cancer screening<br>Follow-up infections, lung transplant, metastases |
| **CTA** | Iodinated contrast highlights vasculature (Scan timed for maximum opacification of vessel being studied) | Contrast can cause severe allergic reaction and is nephrotoxic | Yes | PE<br>Aortic aneurysms<br>Aortic dissection |

# Lung Abnormalities

## Atelectasis

- pathogenesis: collapse of lung tissue due to restricted breathing, blockage of bronchi, external compression, or poor surfactant
- findings
  - increased opacity of involved segment/lobe, vascular crowding, silhouette sign, air bronchograms
  - volume loss: fissure deviation, hilar/mediastinal displacement, diaphragm elevation
  - compensatory hyperinflation of remaining normal lung
- differential diagnosis
  - obstructive (most common): air distal to obstruction is reabsorbed causing alveolar collapse
- post-surgical, endobronchial lesion, foreign body, inflammation (granulomatous infections, pneumoconiosis, sarcoidosis, radiation injury), or mucous plug (cystic fibrosis)
  - compressive
  - tumour, bulla, effusion, enlarged heart, lymphadenopathy
  - traction (cicatrization): due to scarring, which distorts alveoli and contracts the lung
  - adhesive: due to lack of surfactant
- hyaline membrane disease, prematurity
  - passive (relaxation): a result of air or fluid in the pleural space
- pleural effusion, pneumothorax
- management: in the absence of a known etiology, persisting atelectasis must be investigated (i.e. CT thorax) to rule out a bronchogenic carcinoma

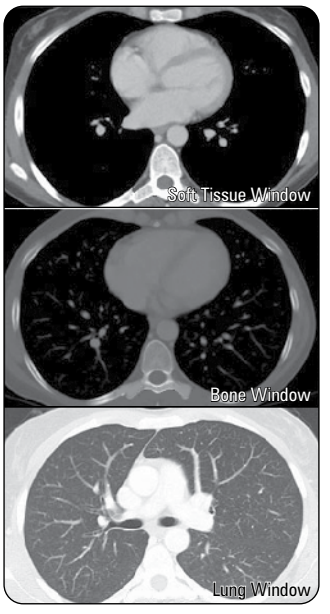



**Figure 4. CT thorax windows**

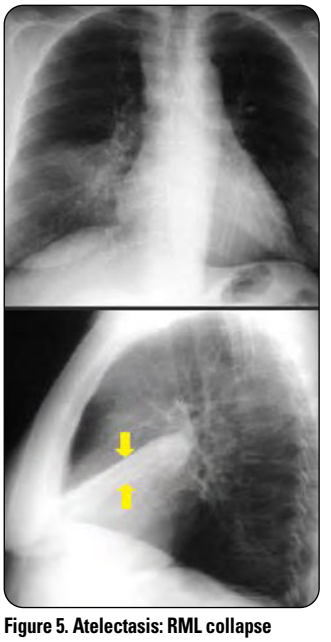


**Figure 5. Atelectasis: RML collapse**

**DDx of Airspace Disease**

- Pus (e.g. infections such as pneumonia)
- Fluid (e.g. pulmonary edema)
- Blood (e.g. pulmonary hemorrhage)
- Cells (e.g. bronchioalveolar carcinoma, lymphoma)
- Protein (e.g. alveolar proteinosis)

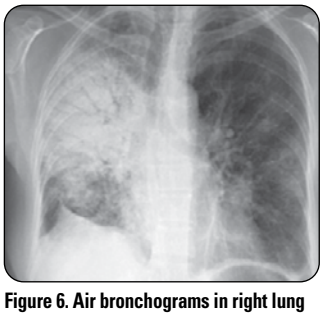


**Figure 6. Air bronchograms in right lung**

## Consolidation

- pathogenesis: fluid (water, blood), inflammatory exudates, protein, or tumour in alveoli
- findings
  - air bronchograms: lucent branching bronchi visible through opacification
  - airspace nodules: fluffy, patchy, poorly defined margins with later tendency to coalesce, may take on lobar or segmental distribution
  - silhouette sign
- differential diagnosis
  - fluid: pulmonary edema, blood (trauma, vasculitis, bleeding disorder, pulmonary infarct)
  - inflammatory exudates: bacterial infections, TB, allergic hypersensitivity alveolitis, COP (cryptogenic organizing pneumonia), allergic bronchopulmonary aspergillosis, aspiration, sarcoidosis
  - protein: pulmonary alveolar proteinosis
  - tumour: bronchoalveolar carcinoma, lymphoma
- management: varies depending on the pattern of consolidation, which can suggest different etiologies; should also be done in the context of clinical picture

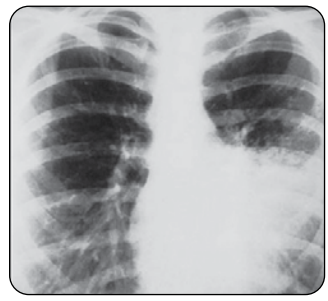


**Figure 7. Consolidation: bacterial pneumonia**

## Interstitial Disease

- pathogenesis: pathological process involving the interlobular connective tissue (i.e. "scaffolding of the lung")
- findings
  - septal thickening: fine lines caused by thickened connective tissue septae (most commonly due to pulmonary edema or lymphangitis carcinomatosis)
  - these manifest on Chest X-ray as:
    - Kerley A: long thin lines in upper lobes
    - Kerley B: short horizontal lines extending from lateral lung margin
    - Kerley C: diffuse linear pattern throughout lung
  - nodular: 1-5 mm well-defined nodules distributed evenly throughout lung
    - seen in malignancy, pneumoconiosis, and granulomatous disease (e.g. sarcoidosis, miliary TB)
  - reticular: fine curvilinear opacities
    - seen in interstitial lung diseases (pulmonary fibrosis)
    - watch for pneumothorax as a complication
  - reticulonodular: combination of reticular and nodular patterns
  - may also see signs of airspace disease (atelectasis, consolidation)
- differential diagnosis
  - occupational/environmental exposure
    - inorganic: asbestosis, coal miner's pneumoconiosis, silicosis, berylliosis, talc pneumoconiosis
    - organic: hypersensitivity pneumonitis, bird fancier's lung, farmer's lung (mouldy hay), and other organic dust
  - autoimmune: connective tissue diseases. (e.g. rheumatoid arthritis, scleroderma, SLE, polymyositis, mixed connective tissue disease), IBD, celiac disease, vasculitis
  - drug-related: antibiotics (cephalosporins, nitrofurantoin), NSAIDs, phenytoin, carbamazepine, fluoxetine, amiodarone, chemotherapy (e.g. methotrexate), heroin, cocaine, methadone
  - infections: non-tuberculous mycobacteria, certain fungal infections
  - idiopathic: hypersensitivity pneumonitis, IPF
  - for Causes of *Interstitial Lung Disease* Classified by Distribution, see Respirology, R13
  - management: high-resolution CT thorax and ± biopsy

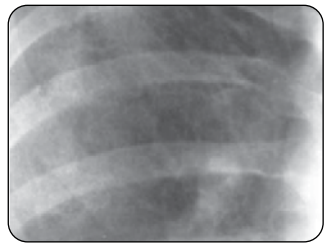


**Figure 8. Interstitial disease: fine reticular pattern**

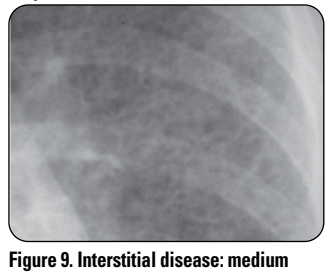


**Figure 9. Interstitial disease: medium reticular pattern**

## Pulmonary Nodule

- findings
  - round opacity ± silhouette sign
  - note: do not mistake nipple shadows for nodules; if in doubt, repeat CXR with nipple markers
- differential diagnosis
  - extrapulmonary density: nipple, skin lesion, electrode, pleural mass, bony lesion
  - solitary nodule
- tumour: carcinoma, hamartoma, metastasis, bronchial adenoma
- inflammation: histoplasmoma, tuberculoma, coccidioidomycosis
- vascular: AV fistula, pulmonary varix (dilated pulmonary vein), infarct, embolism
  - multiple nodules: metastases, abscess, granulomatous lung disease (TB, fungal, sarcoid, rheumatoid nodules, silicosis, GPA)
- management: clinical information and CT appearance determine level of suspicion of malignancy
  - if high probability of malignancy, invasive testing (fine needle aspiration, transbronchial/transthoracic biopsy) is indicated
  - if low probability of malignancy, follow-up imaging as per Fleischner guidelines 2017



**DDx of Interstitial Lung Disease**

**FASSTEN (upper lung disease)**
**F**armer's lung (hypersensitivity pneumonitis)
**A**nkylosing spondylitis
**S**arcoidosis
**S**ilicosis
**T**B
**E**osinophilic granuloma (Langerhans cell histiocytosis)
**N**eurofibromatosis

**BAD RASH (lower lung disease)**
**B**OOP
**A**sbestos
**D**rugs (nitrofurantoin, hydralazine, isoniazid, amiodarone, many chemotherapy drugs)
**R**heumatological disease
**A**spiration
**S**cleroderma
**H**amman Rich (IPF) and idiopathic pulmonary fibrosis



**DDx for Cavitating Lung Nodule**

**WEIRD HOLES**
GPA (**W**egener's)
**E**mbolic (pulmonary, septic)
**I**nfection (anaerobes, pneumocystis, TB)
**R**heumatoid (necrobiotic nodules)
**D**evelopmental cysts (sequestration)
**H**istiocytosis
**O**ncological
**L**ymphangioleiomyomatosis
**E**nvironmental, occupational
**S**arcoidosis

**Table 5. Characteristics of Benign and Malignant Pulmonary Nodules**

| | Malignant | Benign |
|---|---|---|
| **Margin** | Ill-defined/spiculated ("corona radiata") | Well-defined |
| **Contour** | Lobulated | Smooth |
| **Calcification** | Eccentric or stippled | Diffuse, central, popcorn, concentric |
| **Doubling Time** | 20-460 d | <20 d or >460 d |
| **Other Features** | Cavitation, collapse, adenopathy, pleural effusion, lytic bone lesions, smoking history | |
| **Size** | >3 cm | <3 cm |
| **Cavitation** | Yes, especially with wall thickness >15 mm, eccentric cavity, and shaggy internal margins | No |
| **Satellite Lesions** | No | Yes |



**Figure 10. Pulmonary nodule: bronchogenic carcinoma**

# Pulmonary Vascular Abnormalities

## Pulmonary Edema

- pathogenesis: fluid accumulation in the airspaces of the lungs
- findings
  - vascular redistribution/enlargement, cephalization, pleural effusion, cardiomegaly (may be present in cardiogenic edema and fluid overloaded states)
  - fluid initially collects in interstitium
- loss of definition of pulmonary vasculature
- peribronchial cuffing
- Kerley B lines
- reticulonodular pattern
- thickening of interlobar fissures
  - as pulmonary edema progresses, fluid collects in alveoli and causes diffuse airspace disease, often in a "bat wing" or "butterfly" pattern in perihilar regions (outermost lung fields tend to be spared)
- differential diagnosis: cardiogenic (e.g. CHF), renal failure, volume overload, non-cardiogenic (e.g. ARDS)

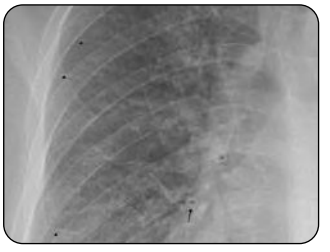


**Figure 11. Peribronchial cuffing**

## Pulmonary Embolism

- pathogenesis: arterial blockage in the pulmonary arteries due to emboli from pelvic or leg veins, rarely from PICC lines, ports, air, fat, or amniotic fluid
- findings
  - generally not possible to definitively diagnose on plain film. Diagnosis made by CT pulmonary angiogram or Ventilation/perfusion scinticraphy. (VQ scan)
  - CXR: Westermark sign (localized pulmonary oligemia), Hampton's hump (triangular peripheral infarct), enlarged right ventricle and right atrium, atelectasis, pleural effusion, and rarely pulmonary edema
  - definitive imaging study: CT pulmonary angiography to look for filling defect in contrast-filled pulmonary arteries
  - VQ scan: Can be used in patients with impaired renal function or in pregnancy

# Pleural Abnormalities

## Pleural Effusion

**Table 6. Sensitivity of Plain Film Views for Pleural Effusion**

| X-Ray Projection | Minimum Volume to Visualize |
|---|---|
| **Lateral decubitus** | 25 mL: most sensitive |
| **Upright lateral** | 50 mL: meniscus seen in the posterior costophrenic sulcus |
| **PA** | 200 mL |
| **Supine** | Diffuse haziness |

- a horizontal fluid level is seen only in a hydropneumothorax (i.e. both fluid and air within pleural cavity)
- effusion may exert mass effect, shift trachea and mediastinum to opposite side, or cause atelectasis of adjacent lung
- U/S is superior to plain film for detection of small effusions and may also aid in thoracentesis; POCUS is now standard of care in acute situations

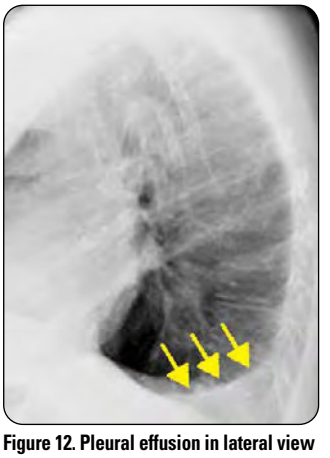


**Figure 12. Pleural effusion in lateral view**

### Pneumothorax

- pathogenesis: gas/air accumulation within the pleural space resulting in separation of the lung from the chest wall
- findings
  - upright chest film allows visualization of visceral pleura as curvilinear line paralleling chest wall, separating partially collapsed lung from pleural air. Occasional tracheal deviation to side of pneumothorax, except in tension pneumothorax
  - more obvious on expiratory (increased contrast between lung and air) or lateral decubitus films (air collects superiorly)
  - more difficult to detect on supine film; look for the "deep (costophrenic) sulcus" sign, "double diaphragm" sign (dome and anterior portions of diaphragm outlined by lung and pleural air, respectively), hyperlucent hemithorax, sharpening of adjacent mediastinal structures
  - mediastinal shift may occur in tension pneumothorax
- differential diagnosis: spontaneous (tall and thin males, smokers), iatrogenic (lung biopsy, ventilation, central venous catheter insertion), trauma (associated with rib fractures), emphysema, malignancy, honeycomb lung
- management: needle decompression in 2nd ICS midclavicular line or chest tube insertion in 5th ICS anterior axillary line, repeat CXR to ensure resolution

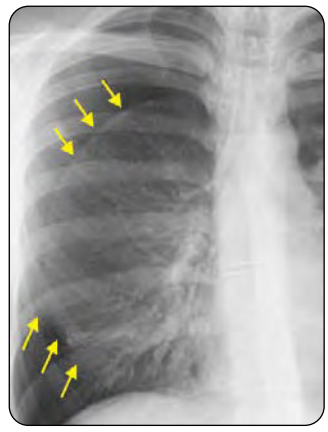


**Figure 13. Pneumothorax**

### Asbestos

- asbestos exposure may cause various pleural abnormalities including benign plaques (most common; these may calcify), diffuse pleural fibrosis, effusion, and malignant mesothelioma

## Mediastinal Abnormalities

### Mediastinal Mass

- the mediastinum is divided into four compartments; this provides an approach to the differential diagnosis of a mediastinal mass
- anterior border formed by the sternum and posterior border by the heart and great vessels
  - 4 Ts: thyroid, thymic neoplasm, teratoma, terrible lymphoma
  - cardiophrenic angle mass differential: thymic cyst, epicardial fat pad, foramen of Morgagni hernia
- middle border (extending behind anterior mediastinum to a line 1 cm posterior to the anterior border of the thoracic vertebral bodies)
  - esophageal carcinoma, esophageal duplication cyst, metastatic disease, lymphadenopathy (all causes), hiatus hernia, bronchogenic cyst
- posterior border (posterior to the middle line described above)
- neurogenic tumour (e.g. neurofibroma, schwannoma), neurenteric cyst, thoracic duct cyst, lateral meningocele, Bochdalek hernia, extramedullary hematopoiesis
- superior boundaries (superiorly by thoracic inlet, inferiorly by plane of the sternal angle, anteriorly by manubrium, posteriorly by T1-T4, laterally by pleura)
- in addition, any compartment may give rise to lymphoma, lung cancer, aortic aneurysm or other vascular abnormalities, abscess, or hematoma

**Elevated Hemidiaphragm Suggests**
**PAL DIP**
**P**regnancy
**A**telectasis
**L**ung resection
**D**iaphragmatic paralysis
**I**ntra-abdominal process
**P**neumonectomy
**P**leural effusion also may result in apparent elevation

**Depressed Hemidiaphragm Suggests**
**TALC**
**T**umour
**A**sthma
**L**arge pleural effusion
**C**OPD

**DDx Anterior Mediastinal Mass**
**4 Ts**
**T**hyroid
**T**hymic neoplasm
**T**eratoma
**T**errible lymphoma

### Enlarged Cardiac Silhouette

- heart borders
  - on PA view, right heart border is formed by right atrium; left heart border is formed by left atrium and left ventricle
  - on lateral view, anterior heart border is formed by right ventricle; posterior border is formed by left atrium (superior to left ventricle) and left ventricle
- cardiothoracic ratio = greatest transverse dimension of the central shadow relative to the greatest transverse dimension of the thoracic cavity
  - using a good quality erect PA chest film in adults, cardiothoracic ratio of >0.5 is abnormal
  - differential of ratio >0.5
    - cardiomegaly (myocardial dilatation or hypertrophy)
    - pericardial effusion
    - poor inspiratory effort/low lung volumes
    - pectus excavatum
- ratio <0.5 does not exclude enlargement
- pericardial effusion: globular heart with loss of indentations on left mediastinal border
- RA enlargement: increase in curvature of right heart border and enlargement of SVC
- LA enlargement: straightening of left heart border; increased opacity of lower right side of cardiovascular shadow (double heart border); elevation of left main bronchus (specifically, the upper lobe bronchus on the lateral film), distance between left main bronchus and "double" heart border >7 cm, splayed carina (late sign)
- RV enlargement: elevation of cardiac apex from diaphragm; anterior enlargement leading to loss of retrosternal air space on lateral; increased contact of right ventricle against sternum
- LV enlargement: rounding of the cardiac apex; displacement of left cardiac boarder leftward, inferiorly, and posteriorly

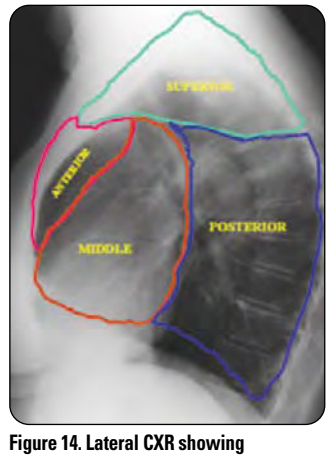



**Figure 14. Lateral CXR showing four mediastinal compartments**

# Tubes, Lines, and Catheters

- ensure appropriate placement and assess potential complications of lines and tubes
- avoid mistaking a line/tube for pathology (e.g. oxygen rebreather mask for pneumothoraces)

### Central Venous Catheter
- used for fluid and medication administration, vascular access for hemodialysis, and CVP monitoring
- Ideally located at the SVC/Atrial junction to prevent inducing arrhythmias or perforating wall of atrium
  - if monitoring CVP, catheter tip must be proximal to venous valves
- tip of well-positioned central venous catheter projects over silhouette of SVC in a zone demarcated superiorly by the anterior first rib end and clavicle, and inferiorly by top of RA
- course should parallel that of the SVC; if appears to bend as it approaches wall of SVC or appears perpendicular, catheter may damage and ultimately perforate wall of SVC
- complications: pneumothorax, bleeding (mediastinal, pleural), air embolism

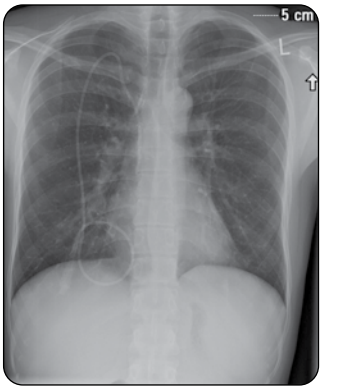


**Figure 15. CXR showing well-positioned central venous catheter**

### Endotracheal Tube
- frontal chest film: tube projects over trachea and shallow oblique or lateral chest radiograph will help determine position in 3 dimensions
- progressive gaseous distention of stomach on repeat imaging is concerning for esophageal intubation
- tip should be located 2-4 cm above tracheal carina (avoids bronchus intubation and vocal cord irritation)
- maximum inflation diameter <3 cm to avoid necrosis of tracheal mucosa and rupture; ensure diameter of balloon is less than tracheal diameter above and below balloon
- complications: aspiration (parenchymal opacities), pharyngeal perforation (subcutaneous emphysema, pneumomediastinum, mediastinitis)

### Nasogastric Tube
- tip and side port should be positioned distal to esophagogastric junction and proximal to gastric pylorus
- radiographic confirmation of tube is mandatory because clinical techniques for assessing tip position may be unreliable
- complications: aspiration (parenchymal opacities), pneumothorax

### Swan-Ganz Catheter
- to monitor pulmonary capillary wedge pressure and estimate diastolic filling of left heart
- tip should be positioned within right or left main pulmonary arteries or in one of their large, lobar branches
- if tip is located more distally, increased risk of prolonged pulmonary artery occlusion resulting in pulmonary infarction or, rarely, pulmonary artery rupture/aneurysm
- complications: pneumothorax, bleeding (mediastinal, pleural), air embolism

### Chest Tube
- in dorsal and caudal portion of pleural space to evacuate fluid
- in ventral and cephalad portions of pleural space to evacuate pneumothoraces
- tube may lie in fissure as long as functioning
- complications: bleeding, infection, lung laceration

# Abdominal Imaging

## Abdominal X-Ray

**3 Views of AXR**
- Erect/Upright
- Supine
- Left lateral decubitus

### Indications
- acute abdomen: bowel perforation, toxic megacolon, bowel ischemia, small bowel obstruction, large bowel obstruction
- chronic symptoms: constipation, calcifications (gallstones, renal stones, urinary bladder stones, etc.)
- not useful in: GI bleeds, chronic anemia, vague GI symptoms

### Anatomy
- abdomen divided into 2 cavities:
  - peritoneal cavity: lined by peritoneum that wraps around most of the bowel, the spleen, and most of the liver; forms a recess lateral to both the ascending and descending colon (paracolic gutters)
  - retroperitoneal cavity: contains several organs situated posterior to the peritoneal cavity; the contour of these can often be seen on radiographs

**Table 7. Differentiating Small and Large Bowel**

| Property | Small Bowel | Large Bowel |
|---|---|---|
| **Mucosal Folds** | Uninterrupted valvulae conniventes (or plicae circularis) | Interrupted haustra extend only partway across lumen |
| **Location** | Central | Peripheral (picture frame) |
| **Maximum Diameter** | 3 cm | 6 cm (9 cm at cecum) |
| **Maximum Fold Thickness** | 3 mm | 5 mm |
| **Other** | Rarely contains solid fecal material | Commonly contains solid fecal material |

**3-6-9 Rule of Dilation**
Small bowel (>3 cm)
Large bowel (>6 cm)
Cecum (>9 cm)

# Approach to Abdominal X-Ray

- mnemonic: "Free ABDO"
- "Free": free air and fluid
  - free fluid
    - small amounts of fluid: increased distance between lateral fat stripes and adjacent colon may indicate free peritoneal fluid in the paracolic gutters
    - large amounts of fluid: diffuse increased opacification on supine film; bowel floats to centre of anterior abdominal wall
    - ascites and blood (hemoperitoneum) are the same density on the radiograph, and therefore, cannot be differentiated
    - free intraperitoneal air suggests rupture of a hollow viscus (anterior duodenum, transverse colon), penetrating trauma, or recent (<7 d) surgery
- "A": air in the bowel (can be normal, ileus, or obstruction)
  - volvulus – twisting of the bowel upon itself; from most to least common:
    - **sigmoid**: "coffee bean" sign (massively dilated sigmoid projects to right or mid-upper abdomen) with proximal dilation
    - cecal: massively dilated bowel loop projecting to left or mid-upper abdomen with small bowel dilation
    - gastric: rare
    - transverse colon: rare (usually young individuals)
    - small bowel: "corkscrew sign" (rarely diagnosed on plain films, seen best on CT)
  - toxic megacolon
    - manifestation of fulminant colitis
    - extreme dilatation of colon (>6.5 cm) with mucosal changes (e.g. foci of edema, ulceration, pseudopolyps), loss of normal haustral pattern
- "B": bowel wall thickening
  - increased soft tissue density in bowel wall, thumb-like indentations in bowel wall ("thumb-printing"), or a picket-fence appearance of the valvulae conniventes ("stacked coin" appearance)
  - may be seen in IBD, infection, ischemia, hypoproteinemic states, and submucosal hemorrhage
- "D": densities
  - bones: look for gross abnormalities of lower ribs, vertebral column, and bony pelvis
  - abnormal calcifications: approach by location
    - RUQ: renal stone, adrenal calcification, gallstone, porcelain gallbladder
    - RLQ: ureteral stone, appendicolith, gallstone ileus
    - LUQ: renal stone, adrenal calcification, tail of pancreas
    - LLQ: ureteral stone
    - central: aorta/aortic aneurysm, pancreas, lymph nodes
    - pelvis: phleboliths (i.e. calcified veins), uterine fibroids, bladder stones
- "O": organs
  - kidney, liver, gallbladder, spleen, pancreas, urinary bladder, psoas shadow
  - outlines can occasionally be identified because they are surrounded by more lucent fat, but all are best visualized with other imaging modalities (CT, MRI)

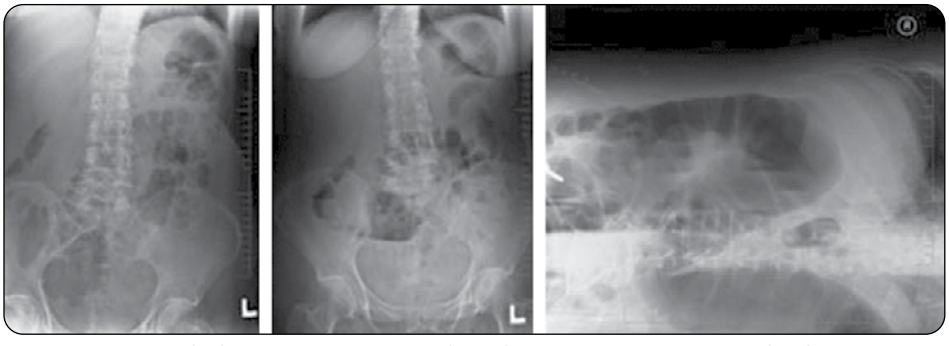


**Figure 16. Normal AXRs: (left) supine anteroposterior AXR, (middle) upright anteroposterior AXR, and (right) left lateral decubitus AXR**

**Biliary vs. Portal Venous Air**
"Go with the flow": air follows the flow of bile or portal venous blood
Biliary air is most prominent centrally over the liver
Portal venous air is most prominent peripherally

**Table 8. Abnormal Air on Abdominal X-Ray**

| Air | Appearance | Common Etiologies |
|---|---|---|
| **Extraluminal**<br>Intraperitoneal (pneumoperitoneum) | Upright film: air under diaphragm<br>Left lateral decubitus film: air between liver and abdominal wall<br>Supine film: gas outlines of structures not normally seen:<br>Inner and outer bowel wall (Rigler's sign)<br>Falciform ligament<br>Peritoneal cavity ("football" sign) | Perforated viscus<br>Post-operative (up to 10 d to be resorbed) |
| Retroperitoneal | Gas outlining retroperitoneal structures allowing increased visualization:<br>Psoas shadows<br>Renal shadows | Perforation of retroperitoneal segments of bowel: duodenal ulcer, post-colonoscopy |
| **Intramural** (pneumatosis intestinalis) | Lucent air streaks in bowel wall, 2 types:<br>1. Linear<br>2. Rounded (cystoides type) | 1. Linear: ischemia, necrotizing enterocolitis<br>2. Rounded/cystoides (generally benign): primary (idiopathic), secondary to COPD |
| **Intraluminal** | Dilated loops of bowel, air-fluid levels | Adynamic (paralytic) ileus, mechanical bowel obstruction |
| **Loculated** | Mottled, localized in abnormal position without normal bowel features | Abscess (evaluate with CT) |
| **Biliary** | Air centrally over liver | Sphincterotomy, gallstone ileus, erosive peptic ulcer, cholangitis, emphysematous cholecystitis |
| **Portal Venous** | Air peripherally over liver in branching pattern | Bowel ischemia/infarction |

**Table 9. Adynamic Ileus vs. Mechanical Obstruction**

| Feature | Adynamic Ileus | Mechanical Obstruction |
|---|---|---|
| **Calibre of Bowel Loops** | Normal or dilated | Usually dilated |
| **Air-Fluid Levels** (erect and left lateral decubitus films only) | Same level in the same single loop | Multiple air fluid levels giving "step ladder" appearance, dynamic (indicating peristalsis present), "string of pearls" (row of small gas accumulations in the dilated valvulae conniventes) |
| **Distribution of Bowel Gas** | Air throughout GI tract is generalized or localized<br>In a localized ileus (e.g. pancreatitis, appendicitis), dilated "sentinel loop" remains in the same location on serial films, usually adjacent to the area of inflammation | Dilated bowel up to the point of obstruction (i.e. transition point)<br>No air distal to obstructed segment<br>"Hairpin" (180°) turns in bowel |

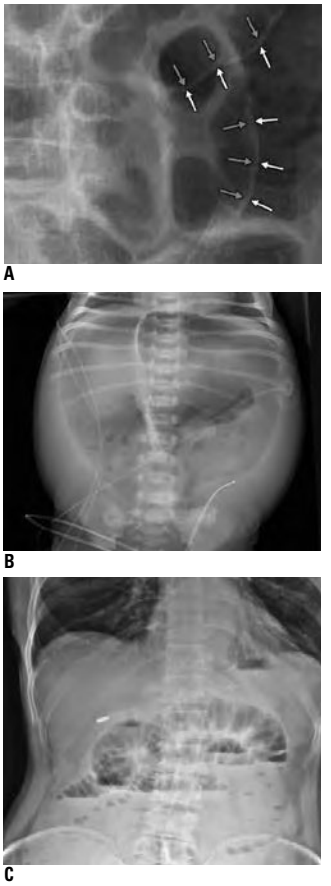


**Figure 17. (A) Rigler's sign (B) "football" sign (C) string of pearls sign**

Rigler's sign courtesy of Dr Jeremy Jones, Radiopaedia.org, rID: 8041. Prof Frank Gaillard https://radiopaedia.org/cases/8041

Football sign courtesy of Dr Maxime St-Amant, Radiopaedia.org, rID: 18597. https://radiopaedia.org/cases/18597

String of pearls courtesy of Dr Maulik S Patel, Radiopaedia.org, rID: 14006. https://radiopaedia.org/cases/14006

# Abdominal Computed Tomography

- indications for plain CT: renal colic, hemorrhage
- indications for CT with contrast:
  - IV contrast given immediately before or during CT to allow identification of arteries and veins
- portal venous phase: indicated for majority of cases
- biphasic (arterial and portal venous phases): liver, pancreas, bile duct tumours
- caution: contrast allergy (may pre-medicate with steroids and antihistamine)
- contraindication: impaired renal function (based on eGFR)
  - oral contrast: barium or water-soluble (water soluble if suspected perforation) given in most cases to demarcate GI tract
  - rectal contrast: given for investigation of colonic lesions

# Approach to Abdominal Computed Tomography

- look through all images in gestalt fashion to identify any obvious abnormalities
- look at each organ or structure individually, from top to bottom, evaluating the size and shape of each area of increased or decreased density
- evaluate the following:
  - soft tissue window
    - liver, gallbladder, spleen, and pancreas
    - adrenals, kidneys, ureters, and bladder
    - stomach, duodenum, small bowel mesentery, and colon/appendix
    - retroperitoneum (aorta, vena cava, and mesenteric vessels; look for adenopathy in vicinity of vessels)
    - peritoneal cavity for fluid or masses
    - abdominal wall and adjacent soft tissue
  - lung window
    - visible lung (bases)
  - bone window
    - vertebrae, spinal cord, and bony pelvis



**Figure 18. Sigmoid volvulus on plain film, "coffee bean sign"**

Courtesy of Dr Henry Knipe, Radiopaedia.org, rID: 28620. https://radiopaedia.org/cases/28620

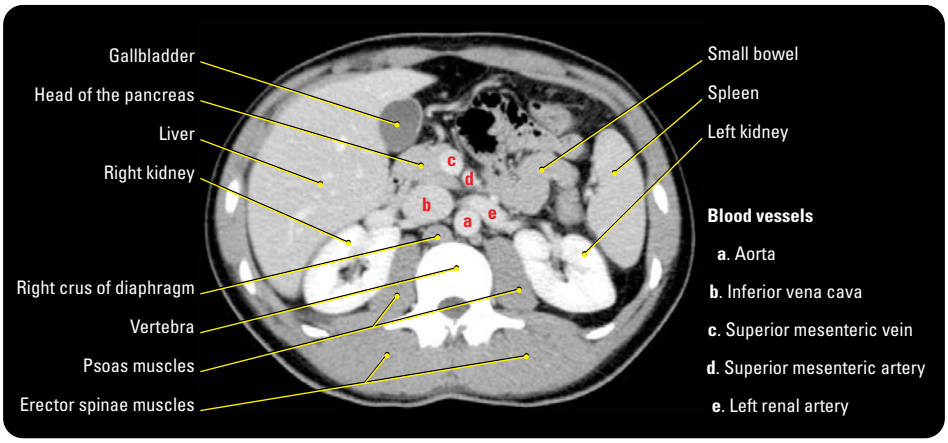



**Figure 19. Axial abdominal computed tomography**

### CT and Bowel Obstruction

- cause of bowel obstruction is rarely found on plain films; CT is the best imaging modality
- the "3,6,9" rule is a very useful guide for determining when the bowel is dilated; the maximum diameter of the bowel is 3 cm for small bowel, 6 cm for large bowel, and 9 cm for cecum; this can also be useful to distinguish small and large bowel, and to assess for 'impending' cecal perforation (e.g. post-untreated Ogilvie's syndrome)
- closed-loop obstruction: an obstruction in two locations (usually small bowel) creating a loop of bowel obstructed both proximally and distally; complications (e.g. ischemia, perforation, necrosis) may occur quickly

### CT Colonography (virtual colonoscopy)

- emerging imaging technique for evaluation of intraluminal colonic masses (i.e. polyps, tumours)
- two CT scans of the abdomen (prone and supine) after the instillation of carbon dioxide into a prepped colon
- computer reconstruction of 2D CT images into a 3D intraluminal view of the colon
- lesions seen on 3D images correlated with 2D axial images
- indications: surveillance in low-risk patients, incomplete colonoscopy, or staging of obstructing colonic lesions

**Colorectal Cancer: CT Colonography and Colonoscopy for Detection-Systematic Review and Meta-Analysis**
Radiology 2011;259:393-405
**Purpose**: To assess the sensitivity of computed tomography (CT) colonography and optical colonoscopy (OC) for colorectal cancer (CRC) detection.
**Methods**: Systematic review and meta-analysis of diagnostic studies evaluating CT colonography detection of CRC based on a priori eligibility criteria, in particular requiring both OC and histological confirmation of disease. Studies that also assessed true-positive and false-negative diagnoses with OC were used to calculate OC sensitivity. Sensitivity of CTC and OC for CRC was the main outcome.
**Results**: 49 studies on 11,151 patients undergoing diagnostic study for detection of CRC were included. CTC has a sensitivity of 96.1% (95% CI 93.8%, 97.7%) and OC has a sensitivity of 94.7% (95% CI 90.4%, 97.2%) for the detection of CRC.
**Conclusion**: CTC is highly sensitive for the detection of CRC and may be a better modality for the initial investigation of suspected CRC, assuming reasonable specificity.

## Contrast Studies

**Table 10. Types of Contrast Studies**

| Study | Organ | Procedure Description | Assessment | Findings |
|---|---|---|---|---|
| **Cine Esophagogram** | Cervical esophagus | Contrast agent swallowed Recorded for later playback and analysis | Dysphagia, swallowing incoordination, recurrent aspiration, post-operative cleft palate repair | Aspiration, webs (partial occlusion), Zenker's diverticulum, cricopharyngeal bar, laryngeal tumour |
| **Barium Swallow** | Thoracic esophagus | Contrast agent swallowed under fluoroscopy, selective images captured | Dysphagia, rule out GERD, post-esophageal surgery | Achalasia, hiatus hernia, esophagitis, cancer, esophageal tear |
| **Upper GI Series** | Thoracic esophagus, stomach, and duodenum | Double contrast study:<br>1. Barium to coat mucosa<br>2. Gas pills for distention<br>Patient NPO after midnight | Dyspepsia, investigate possible upper GI bleed, weight loss/ anemia, post-gastric surgery | Ulcers, neoplasms, filling defects |
| **Enterography and Enteroclysis (MRI or CT)** | Entire small bowel | Enterography: patient drinks 1-2 L of sorbitol, psyllium, or barium solution to distend small bowel<br>Enteroclysis: NJ tube used to pump barium, psyllium, or sorbitol contrast media directly into small bowel | IBD, malabsorption, weight loss/anemia, Meckel's diverticulum | Neoplasms, IBD, malabsorption, infection |

# Specific Visceral Organ Imaging

- for the management of urgent and emergent peritoneal masses, see, General Surgery, GS20

## Liver

- U/S: assessment of cysts, abscesses, tumours, biliary tree
- CT ± IV: most popular procedure for imaging the liver parenchyma (primary liver tumours, metastases, cysts, abscesses, trauma, cirrhosis)
- MR: also excellent in evaluation of primary liver tumours, liver metastases, other parenchymal conditions, and is particularly helpful in differentiating common benign hepatic hemangiomas from primary liver tumours and metastases
- elastography: measures shear wave velocity by U/S (Fibroscan) or MRI (MR elastography) to non-invasively quantify liver fibrosis
- findings:
  - advanced cirrhosis: liver small and irregular (fibrous scarring, segmental atrophy, regenerating nodules)
  - portal HTN: increased portal vein diameter, collateral veins, splenomegaly (≥12 cm), portal vein thrombosis, recanalization of the umbilical vein
  - porto-systemic shunts: caput medusae, esophageal varices, spontaneous spleno-renal shunt
  - U/S: cirrhosis appears nodular and hyperechoic with irregular areas of atrophy of the right lobe and hypertrophy of the caudate or left lobes
  - CT: fatty infiltration appears hypodense
- in order to be visualized, some masses require contrast
- upon identifying a liver lesion on imaging (e.g. U/S), the follow-up imaging modality should be CT or MR. CT would be four-phase non-contrast, arterial, venous, and delayed to distinguish the common benign liver lesion hemangioma from other tumours

Normal liver appears more dense than spleen on CT. If less dense, suspect fatty infiltration

**Liver Mass DDx**

**5 Hs**
**H**CC
**H**ydatid cyst
**H**emangioma
**H**epatic adenoma
**H**yperplasia (focal nodular)

**Table 11. Imaging of Liver Masses**

| Mass | U/S | CT |
|---|---|---|
| **Benign** | | |
| **Hepatic Adenoma** | Well-defined mass with hyperechoic areas due to hemorrhage | Well-defined hypervascular lesion with enlarged central vessel becoming slightly isoattenuating in venous phase |
| **Hemangioma** | Homogeneous hyperechoic mass | Peripheral globular enhancement in arterial phase scans; central filling and persistent enhancement on delayed scans |
| **Focal Nodular Hyperplasia** | Well-defined mass, central scar seen in 50% of cases | Hypervascular mass in arterial phase and isoattenuation to liver in portal venous phase |
| **Abscess** | Ill-defined, irregular margin, hypoechoic contents | Low attenuation lesion with an irregular enhancing wall |
| **Hydatid Cyst** | Simple/multiloculated cyst | Low attenuation simple or multiloculated cyst; calcification |
| **Malignant** | | |
| **HCC** | Single/multiple masses, or diffuse infiltration | Hypervascular; enhances in arterial and washes out in venous phase with portal venous tumour thrombus |
| **Metastases** | Multiple masses of variable echotexture | Usually low attenuation on contrast-enhanced scan |

**Revised Estimates of Diagnostic Test Sensitivity and Specificity in Suspected Biliary Tract Disease**
Arch Intern Med 1998;154:2573-2581
**Purpose**: To assess the sensitivity and specificity of tests used to diagnose cholelithiasis and acute cholecystitis, including ultrasonography (U/S), oral cholecystography, radionucleotide scanning with Technetium, magnetic resonance imaging (MRI) or computed tomography (CT).
**Methods**: Meta-analysis of studies evaluating the use of different imaging modalities in the diagnosis of biliary tract disease. Main outcomes were sensitivity and specificity of the different imaging modalities, using the gold standard of surgery, autopsy, or 3 mo clinical follow-up for cholelithiasis. For acute cholecystitis, pathologic findings, confirmation of an alternate disease, or clinical resolution during hospitalization for cholecystitis were used as the standard.
**Results**: Thirty studies were included. For evaluating cholelithiasis, U/S had the best unadjusted sensitivity (0.97; 95% CI 0.95-0.99) and specificity (0.95, 0.88-1.00) and adjusted (for verification bias) sensitivity (0.84; 0.76-0.92) and specificity (0.99; 95% CI 0.97-1.00). For evaluating acute cholecystitis, radionucleotide scanning has the best sensitivity (0.97; 0.96-0.98) and specificity (0.90; 0.86-0.95).
**Conclusion**: U/S is the test of choice for diagnosing cholelithiasis and radionucleotide scanning is the superior test for diagnosing acute cholecystitis.

## Spleen

- U/S, CT, nuclear medicine scan (nuclear medicine only to distinguish ectopic splenic tissue from enhancing tumours)
- CT for splenic trauma (hemorrhage)

## Pancreas

- tumours
  - U/S: mass is more echogenic than normal pancreatic tissue
  - CT: preferred modality for diagnosis/staging
- ductal dilation secondary to stone/tumour
  - MRCP: imaging of ductal system using MRI cholangiography; no therapeutic potential
  - ERCP: endoscope to inject dye into the biliary tree and x-ray imaging to assess pancreatic and biliary ducts; therapeutic potential (stent placement, stone retrieval)
    - acute pancreatitis is a complication in 5% of diagnostic procedures and 10% of therapeutic procedures

## Biliary Tree

- U/S: bile ducts usually visualized only if dilated, secondary to obstruction (e.g. choledocholithiasis, benign stricture, mass)
- CT: dilated intrahepatic ductules seen as branching, tubular structures following pathway of portal venous system
- MRCP, ERCP, PTC: further evaluation of obstruction and possible intervention

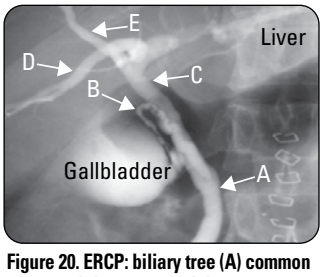



**Figure 20. ERCP: biliary tree (A) common bile duct (B) cystic duct (C) common hepatic duct (D) right hepatic duct (E) left hepatic duct**

# "itis" Imaging

## Acute Cholecystitis

- pathogenesis: inflammation of gallbladder resulting from sustained gallstone impaction in cystic duct, or in the case of acalculous cholechystitis, due to gallbladder ischemia or cholestasis (see General Surgery, GS52)
- best imaging modality: U/S (best sensitivity and specificity); nuclear medicine (HIDA scan) can help diagnose cases of acalculous or chronic cholecystitis
- findings: most sensitive findings are presence of gallstones and positive sonographic Murphy's sign (tenderness from pressure of U/S probe over visualized gallbladder). Secondary findings include thickened gallbladder wall (>3 mm), dilated gallbladder, and pericholecystic fluid
- management: admit, NPO, IVF, analgesia, cefazolin, and early laparoscopic cholecystectomy

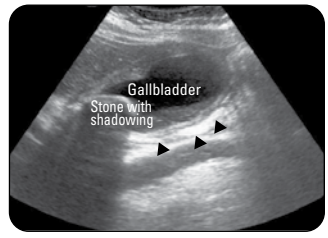



**Figure 21. Ultrasound: Longitudinal view of an inflamed Gallbladder. Arrow heads show thickened walls and pericholecystic fluid**

## Acute Appendicitis

- pathogenesis: luminal obstruction → bacterial overgrowth → inflammation/swelling → increased pressure → localized ischemia → gangrene/perforation → localized abscess or peritonitis (see General Surgery, GS32)
- best imaging modality: U/S or CT
- findings
  - U/S: thick-walled appendix, appendicolith, dilated fluid-filled appendix, non-compressible; may also demonstrate other causes of RLQ pain (e.g. ovarian abscess, IBD, ectopic pregnancy)
  - CT: enlargement of appendix (>6 mm in outer diameter), enhancement of appendiceal wall, adjacent inflammatory stranding, appendicolith; also facilitates percutaneous abscess drainage
- management: admit, NPO, IVF, analgesia, cefazolin + metronidazole, and appendectomy

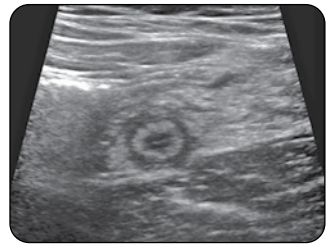


**Figure 22. Ultrasound: inflamed appendix**

## Acute Diverticulitis

- pathogenesis: erosion of the intestinal wall (most commonly rectosigmoid) by increased intraluminal pressure or inspissated food particles → inflammation and focal necrosis → micro- or macroscopic perforation (see General Surgery, GS36)
- best imaging modality: CT, although U/S is sometimes used
- contrast: oral and rectal contrast given before CT to opacify bowel
- findings:
  - cardinal signs: thickened wall, mesenteric infiltration, gas-filled diverticula, abscess
  - CT can be used for percutaneous abscess drainage before or in lieu of surgical intervention
  - sometimes difficult to distinguish from perforated cancer (send abscess fluid for cytology and follow-up with colonoscopy)
  - if chronic, may see fistula (most common to bladder) or sinus tract (linear or branching structures)
- management: ranges from antibiotic treatment to surgical intervention; can use imaging to follow progression

**Computed Tomography and Ultrasonography to Detect Acute Appendicitis in Adults and Adolescents**
Ann Intern Med 2004;141:537-546
**Purpose**: To review the diagnostic accuracy of computed tomography (CT) and ultrasonography (U/S) in the diagnosis of acute appendicitis.
**Methods**: Meta-analysis of prospective studies evaluating the use of CT or U/S, followed by surgical or clinical follow-up in patients with suspected appendicitis. Patients aged ≥14 yr with a clinical suspicion of appendicitis were eligible. Sensitivity and specificity using surgery or clinical follow-up as the gold standard were the main outcomes studied.
**Results**: Twenty-two studies were included. CT (12 studies) had an overall sensitivity of 0.94 (95% CI 0.91-0.95) and a specificity of 0.95 (0.93-0.96). U/S (14 studies) had an overall sensitivity of 0.86 (0.83-0.88) and a specificity of 0.81 (0.78-0.84).
**Conclusion**: CT is more accurate for diagnosing appendicitis in adults and adolescents, although verification bias and inappropriate blinding of reference standards were noted in the included studies.

## Acute Pancreatitis

- pathogenesis: activation of proteolytic enzymes within pancreatic cells leading to local and systemic inflammatory response (see Gastroenterology, G46); a clinical/biochemical diagnosis
- best imaging modality: imaging used to support diagnosis and evaluate for complications (diagnosis cannot be excluded by imaging alone)
  - U/S good for screening and follow-up
  - CT is useful in advanced stages and in assessing for complications (1st line imaging test)
- findings:
  - U/S: hypoechoic enlarged pancreas (if ileus present, gas obscures pancreas)
  - CT: enlarged pancreas, edema, fat stranding with indistinct fat planes, mesenteric and Gerota's fascia (renal fascia) thickening, pseudocyst in lesser sac, abscess (gas or thick-walled fluid collection), pancreatic necrosis (low attenuation gas-containing non-enhancing pancreatic tissue), hemorrhage
- management: supportive therapy
  - CT-guided needle aspiration and/or drainage of abscess when clinically indicated
  - pseudocyst may be followed by CT and drained if symptomatic

## Chronic Pancreatitis

- pathogenesis: (see Gastroenterology, G48)
- best imaging modality: MRCP (can show calcification and duct obstruction)
- findings: U/S, CT scan, and MRI may show calcifications, ductal dilatation, enlargement of the pancreas and fluid collections (e.g. pseudocysts) adjacent to the gland

# Angiography of Gastrointestinal Tract

- anatomy of the arterial branches of the GI tract
  - celiac artery: hepatic, splenic, gastroduodenal, left/right gastric
  - superior mesenteric artery: jejunal, ileal, ileo-colic, right colic, middle colic
  - inferior mesenteric artery: left colic, superior rectal
- imaging modalities
  - conventional angiogram: invasive (usual approach via femoral puncture), catheter used
- flush aortography: catheter injection into abdominal aorta, followed by selective arteriography of individual vessels
  - CT angiogram: modality of choice, non-invasive using IV contrast (no catheterization required)

**Angiography requires active blood loss**
1-1.5 mL/min under optimal conditions for a bleeding site to be visualized in cases of lower GI bleeding

# Genitourinary System and Adrenal

## Urological Imaging

### KUB (Kidney, Ureter, and Bladder X-ray)

- a frontal supine radiograph of the abdomen
- indication: useful in evaluation of radio-opaque renal stones (all stones types except for uric acid and indinavir), indwelling ureteric stents/catheters, and foreign bodies in abdomen
- findings: addition of IV contrast excreted by the kidney (intravenous urogram) allows better visualization of the urinary tract, but has been largely replaced by CT urography

**Imaging Modality Based on Presentation**
- Acute testicular pain = Doppler, U/S
- Amenorrhea = U/S, MRI (brain)
- Bloating = Plain film/CT (if abnormal)
- Flank pain = U/S, CT
- Hematuria = U/S, Cystoscopy, CT
- Infertility = HSG, MRI
- Lower abdominal mass = U/S, CT
- Lower abdominal pain = U/S, CT
- Renal colic = U/S, KUB, CT
- Testicular mass = U/S
- Urethral stricture = Urethrogram

### Abdominal CT

### Renal Masses

- Bosniak classification for cystic renal masses
- class I-II: benign and can be disregarded
- class IIF: should be followed
- class III-IV: suspicious for malignancy, requiring additional workup

**Table 12. Bozniak Classification for Cystic Renal Masses**

| Classes | Definition |
|---|---|
| **Simple Renal Cysts** | |
| **Class I** | Fluid-attenuating well-defined lesion, no septation, no calcification, no solid components, hair thin wall |
| **Class II** | Same as class I + fine calcification or moderately thickened calcification in septae or walls; also includes hyperdense cysts (<3 cm) that do not enhance with contrast<br>*Class IIF: multiple hairline-thin septa with minimal thickening, no enhancing soft tissue components, completely intrarenal non-enhancing high-attenuating renal lesions >3 cm |
| **Complex Renal Cysts** | |
| **Class III** | Thick irregular walls ± calcifications ± septated, enhancing walls or septa with contrast |
| **Renal Cell Carcinoma** | |
| **Class IV** | Same as class III + soft tissue enhancement with contrast (defined as >10 Hounsfield unit increase, characterizing vascularity) with de-enhancement in venous phase ± areas of necrosis |

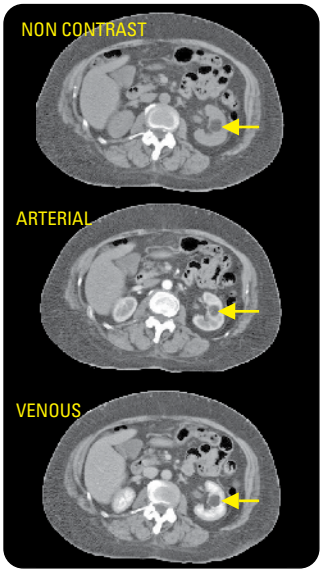



**Figure 23. Triphasic CT of an angiomyolipoma**: showing fat density with non-contrast scan, mildly enhancing with contrast

- plain CT KUB indications: general imaging of renal anatomy, renal colic symptoms, assessment of renal calculi (size and location) and potential sequalae (infection and obstruction), and hydronephrosis prior to urological treatment
- CT urography indications: investigation of cause of hematuria, detailed assessment of urinary tracts (excretory phase), high sensitivity (95%) for uroepithelial malignancies of the upper urinary tracts, assessment of renal calculi
  - phases: unenhanced, excretory
- renal triphasic CT indications: standard imaging for renal masses, allows accurate assessment of renal arteries and veins, better characterization of suspicious renal masses, especially in differentiating renal cell carcinoma from more benign masses, and pre-operative staging
  - phases: unenhanced, arterial and venous (nephrographic), excretory

### Ultrasound

- **indications**: initial study for evaluation of kidney size and nature of renal masses (solid vs. cystic masses, simple vs. complicated cysts); modality of choice for screening patients with suspected hydronephrosis (no IV contrast injection, no radiation to patient, and can be used in patients with renal failure); TRUS useful to evaluate prostate gland and guide biopsies; Doppler U/S to assess renal vasculature
- **findings**: solid renal masses are echogenic (bright on U/S), cystic renal masses have smooth well-defined walls with anechoic interior (dark on U/S), and complicated cysts have internal echoes within a thickened, irregular wall

### Retrograde Pyelography
- indications: visualize the urinary collecting system via a cystoscope, ureteral catheterization, and retrograde injection of contrast medium, visualized by radiograph or fluoroscopy; ordered when the intrarenal collecting system and ureters cannot be opacified using intravenous techniques (patient with impaired renal function, high grade obstruction or allergy to IV contrast)
- findings: only yields information about the collecting systems (renal pelvis and associated structures), no information regarding the parenchyma of the kidney

### Voiding Cystourethrogram
- bladder filled with contrast to the point where voiding is triggered
- fluoroscopy (continuous, real-time X-ray) to visualize bladder during voiding
- indications: males or young females with recurrent UTIs, hydronephrosis, hydroureter, suspected lower urinary tract obstruction, suspected bladder trauma or vesicoureteral reflux
- findings: evaluation of bladder contractility and evidence of vesicoureteral reflux

### Retrograde Urethrogram
- a small Foley catheter placed into penile urethral opening, followed by instillation of contrast and radiographic imaging
- indications: used mainly to study strictures or trauma to the male urethra; first-line study if trauma with blood present at urethral meatus, scrotal hematoma present or high-riding prostate (signs of urethral injury)

### MRI
- advantages: better contrast resolution and tissue discrimination, lack of exposure to ionizing radiation, safer contrast, ability to obtain imaging directly from multiple planes (coronal, sagittal, oblique)
- indications: indicated over CT for depiction of renal masses in patients with previous nephron-sparing surgery, patients requiring serial follow-up (less radiation dosage), patients with reduced renal function, patients with solitary kidneys, clinical staging of prostate cancer (endorectal coil MRI)

### Renal Nuclear Scan

**Table 13. Renal Scan Tests**

| Type of Test | Uses | Radionuclide |
|---|---|---|
| **Renogram** | Assess renal function and collecting system: evaluation of renal failure, workup of urinary tract obstruction and renovascular HTN, investigation of renal transplant | IV $^{99m}$Tc-pentetate (DTPA) or mertiatide (MAG3), and imaged at 1-3 s intervals with a gamma camera over the first 60 s to assess perfusion |
| **Morphological** | Assess renal anatomy: investigation of pyelonephritis and cortical scars | $^{99m}$Tc-DMSA<br>$^{99m}$Tc-glucoheptonate |

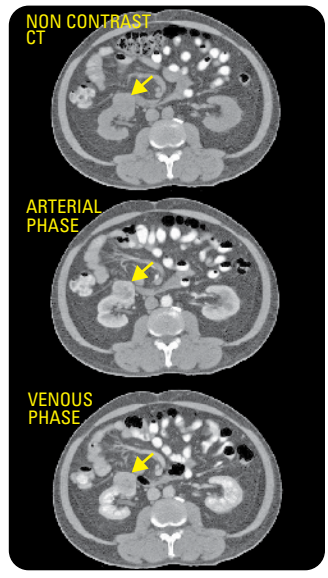



**Figure 24. Triphasic CT of a renal cell carcinoma:** showing arterial enhancing right renal lesion with venous washout (shunting)

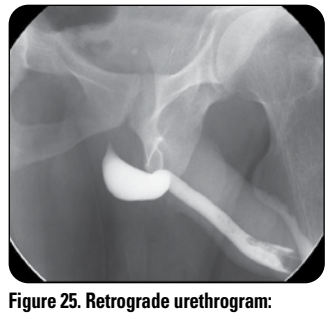


**Figure 25. Retrograde urethrogram: demonstrating stricture in the membranous urethra**

## Gynecological Imaging

### Ultrasound
- transabdominal and transvaginal are the primary modalities, and are indicated for different scenarios
- transabdominal requires a full bladder to push out air-containing loops of bowel
  - indications: good initial investigation for suspected pelvic pathology
- TVUS provides a panoramic pelvic view and enhanced detail of deeper/smaller structures by allowing use of higher frequency sound waves due to reduced distances
  - indications: improved assessment of ovaries, first trimester development, and ectopic pregnancy

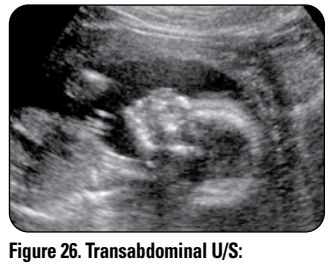


**Figure 26. Transabdominal U/S: pregnancy, 18 wk fetus**

Pregnancy should always be ruled out by β-hCG before CT of a female pelvis (or any organ system) is performed

### Hysterosalpingogram
- performed by x-ray images of the pelvis after cannulation of the cervix and subsequent injection of opacifying agent
- indications: useful for assessing pathology of the uterine cavity and fallopian tubes, evaluating uterine abnormalities (e.g. bicornuate uterus), or evaluation of fertility (absence of flow from tubes to peritoneal cavity indicates obstruction)

### CT/MRI
- indications: evaluating pelvic structures, especially those adjacent to the adnexa and uterus
- invaluable for staging gynecological malignancies and detecting recurrence

### Sonohysterogram
- transcervical saline introduction into uterine cavity to provide enhanced endometrial visualization during TVUS examination
- indications: abnormal uterine bleeding, uterine cavity abnormalities that are suspected or noted on TVUS (e.g. leiomyomas, polyps, synechiae), congenital abnormalities of the uterine cavity, infertility, recurrent pregnancy loss
- contraindications: pregnancy, pelvic infection

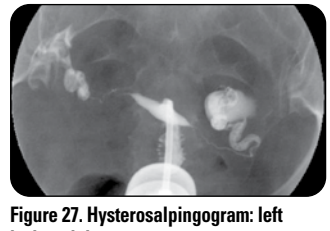


**Figure 27. Hysterosalpingogram: left hydrosalpinx**

**Table 14. Typical and Atypical Findings on a Sonohysterogram**

| Finding | Typical | Atypical |
|---|---|---|
| **Polyps** | A well-defined, homogeneous, polypoid lesion isoechoic to the endometrium with preservation of the endometrial-myometrial interface | Cystic components, multiple polyps, broad base, hypoechogenicity or heterogeneity |
| **Leiomyoma** | Well-defined, broad-based, hypoechoic, solid masses with shadowing. Overlying layer of endometrium is echogenic and distorts the endometrial-myometrial interface | Pedunculation or multilobulated surface |
| **Hyperplasia and Cancer** | Diffuse echogenic endometrial thickening without focal abnormality, although focal lesions can occur. Endometrial cancer is typically a diffuse process, but early cases can be focal and appear as a polypoid mass | |
| **Adhesions** | Mobile, thin, echogenic bands that cut across the endometrial cavity | Thick, broad-based bands that can completely obliterate the endometrial cavity, as in Asherman's syndrome |

# Adrenal Mass

- imaging modality: most often identified on CT scan as 'incidentaloma,' can also use CT/MRI to distinguish benign from malignant masses

**Table 15. Adrenal Mass Findings on CT and MRI**

| Factors | Adrenocortical Adenoma | Adrenocortical Carcinoma | Pheochromocytoma | Metastasis |
|---|---|---|---|---|
| **Diameter (CT)** | Usually ≤3 cm | Usually ≥4 cm | Usually >3 cm | Variable around <3 cm |
| **Shape (CT)** | Smooth margins and round/oval | Irregular with unclear margins | Round/oval with clear margins | Oval/irregular with unclear margins |
| **Texture (CT)** | Homogeneous | Heterogeneous with mixed densities | Heterogeneous with cystic areas | Heterogeneous with mixed densities |
| **Vascularity (CT)** | Not highly vascular | Usually vascular | Usually vascular | Usually vascular |
| **Washout of Contrast Medium on CT** | ≥50% at 10 min | <50% at 10 min | <50% at 10 min | <50% at 10 min |
| **Growth** | Stable or very slow (<1 cm/yr) | Usually rapid (>2 cm/yr) | Slow (0.5-1 cm/yr) | Variable |
| **Other Findings** | Usually low density due to intracellular fat | Necrosis, calcifications, and hemorrhage | Hemorrhage | Occasionally hemorrhage |
| **MRI on T2 Weighted Imaging** | Isointense in relation to liver | Hyperintense in relation to liver | Markedly hyperintense in relation to liver | Hyperintense in relation to liver |

# Neuroradiology

## Modalities

- CT is the modality of choice for most neuropathology; even under circumstances where MRI is preferred
- CT is frequently the initial study performed because of its speed, availability, and lower cost
  - acute craniofacial trauma: CT is best for visualizing "bone and blood"; MRI is used only when CT fails to detect an abnormality despite strong clinical suspicion
  - acute stroke: MRI ideal, CT most frequently used
  - acute headache with focal neurologic signs
  - suspected subarachnoid or intracranial hemorrhage
  - suspected hydrocephalus
  - meningitis: rule out mass effect (e.g. cerebral herniation, shift) prior to lumbar puncture
  - tinnitus and vertigo: CT and MRI are used in combination to detect bony abnormalities and CN VIII tumours, respectively

### Skull Films

- rarely performed, generally not indicated for non-penetrating head trauma
- indications: screening for destructive bony lesions (e.g. metastases), metabolic disease, skull anomalies, post-operative changes and confirmation of hardware placement, skeletal surveys, multiple myeloma

### CT

- indications: excellent study for evaluation of bony and intracranial abnormalities
- often done first without and then with IV contrast to show vascular structures or anomalies



**Modality Based on Neuropathology Presentation**

- Cognitive decline = CT
- Cord compression = MRI
- Decreased level of consciousness = CT
- Fish bone/other swallowed foreign body = CT
- Low back pain, radiculopathy = MRI
- Multiple sclerosis = MRI
- Neck infection = CT
- Orbital infection = CT
- Rule out bleed = CT
- Rule out aneurysm = CTA, MRA
- Seizure = CT
- Sinusitis = CT
- Stroke = CT, MRI
- Trauma = CT
- Weakness, systemically unwell = CT

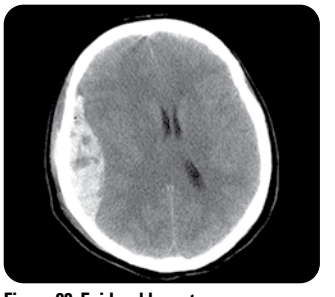


**Figure 28. Epidural hematoma**

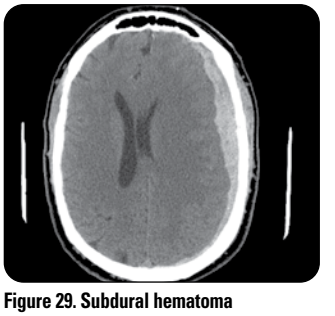


**Figure 29. Subdural hematoma**

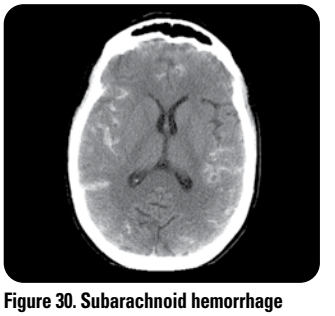


**Figure 30. Subarachnoid hemorrhage**

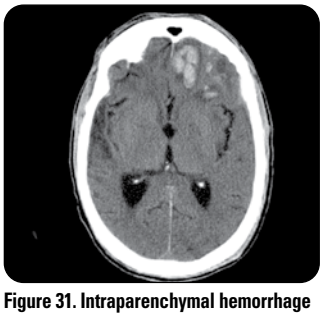


**Figure 31. Intraparenchymal hemorrhage**

- vascular structures and areas of blood-brain barrier impairment are opaque (e.g. hyperattenuating or bright/show enhancement) with contrast injection
  - when in doubt, look for Circle of Willis or confluence of sinuses to determine presence of contrast enhancement
- posterior fossa can be obscured by extensive bony-related streak artifact
- rule out skull fracture, epidural hematoma (lenticular shape), subdural hematoma (crescentic shape), subarachnoid hemorrhage, space-occupying lesion, hydrocephalus, and cerebral edema
- multiplanar imaging can be performed with current generation of multidetector CT scanners

### Myelography
- introduction of water-soluble, low-osmotic contrast media into subarachnoid space via lumbar puncture followed by x-ray
- largely replaced by MRI or CT myelogram
- indications: excellent study for disc herniation, traumatic nerve root avulsion, patients with contraindication to MRI

### MRI
- indications: finer neuroanatomic definition, better grey-white matter differentiation (especially T1-weighted series), better evaluation of edema extent (better tumour detection), allows evaluation of structures obscured by bony artifacts on CT (posterior fossa structures), multiplanar imaging helpful in pre-operative assessment

### Cerebral Angiography/CT Angiography/MR Angiography
- indications: evaluation of vascular lesions such as atherosclerotic disease, aneurysms, vascular malformations, arterial dissections
- conventional digital subtraction angiography remains the gold standard for the assessment of neck and intracranial vessels; however, it is an invasive procedure requiring arterial (femoral) puncture; catheter manipulation confers risk of vessel injury (e.g. dissection, occlusion, vasospasm, emboli)
- MRA methods (phase contrast, time of flight, gadolinium-enhanced) and CTA are much less invasive without risk to intracranial or neck vessels
- MRA and CTA are often used first as 'screening tests' for the assessment of subarachnoid hemorrhage, vasospasm, or aneurysms

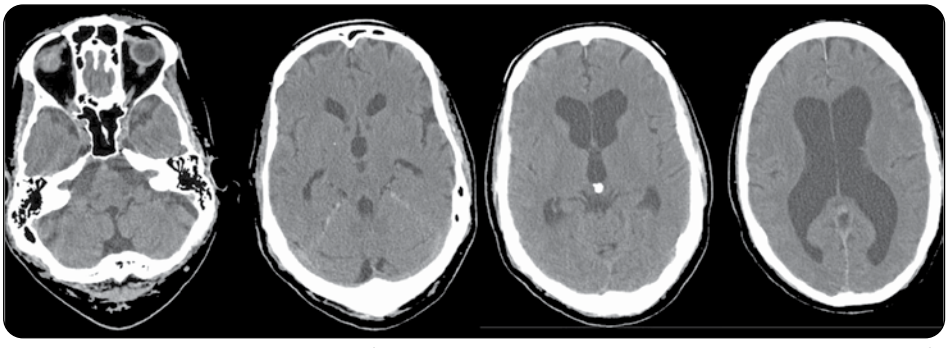


**Figure 32. Hydrocephalus: ventricular dilatation (may see periventricular low attenuation due to transependymal CSF flow)**

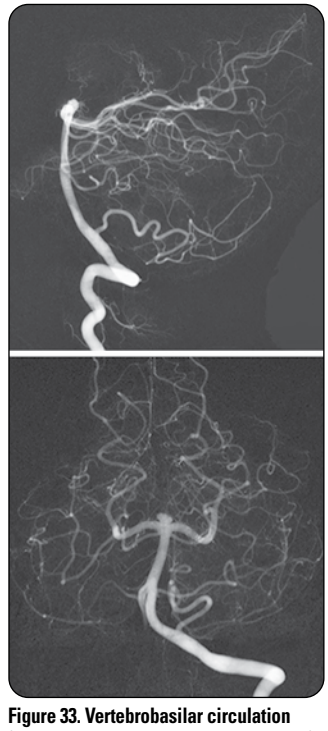


**Figure 33. Vertebrobasilar circulation**
(note the incidental basilar tip aneurysm)

**Table 16. Two Types of Hydrocephalus**

| Type | Cause |
|---|---|
| **Communicating/Extra-Ventricular** | Impaired CSF reabsorption with unobstructed flow in ventricular system; imaging shows all ventricles dilated |
| **Non-Communicating** | Obstruction within the ventricular system (e.g. mass obstructing the aqueduct or foramen of Monro); imaging shows dilatation of ventricles proximal to the obstruction |

### Nuclear Medicine
- SPECT imaging using $^{99m}$Tc-exametazime (HMPAO) and $^{99m}$Tc-bicisate (ECD) assesses cerebral blood flow, as radionuclides diffuse rapidly across the blood brain barrier and become trapped within neurons at a magnitude proportional to cerebral blood flow
- $^{18}$FDG PET imaging assesses cerebral metabolic activity
- indications: differentiation of residual tumour vs. radiation necrosis; localizing of epileptic seizure foci; evaluation of atypical dementia

## Approach to CT Head

- think anatomically, work from superficial to deep
- scan: confirm that the imaging is of the correct patient, whether contrast was used, if the patient is aligned properly, if there is artifact present
- skin/soft tissue: examine the soft tissue superficial to the skull, looking for thickening suggestive of hematoma or edema; also evaluate the ear, orbital contents (globe, fat, muscles), parotid gland, muscles of mastication (masseter, temporalis, pterygoids), visualize pharynx



**Approach to the CT Head**
**Some** = **S**can
**Sore** = **S**kin/**S**oft Tissue
**Brains** = **B**one/Airspace
**Demonstrate** = **D**ura/Subdural space
**Pushed** = **P**arenchyma
**Ventricles** = **V**entricles/Sulci/Cisterns



Transient ischemic attacks are not associated with radiological findings

- bone and airspace (use the bone window): check calvarium, visualize mandible, visualize C-spine (usually C1 and maybe part of C2) for fractures, absent bone, lytic/sclerotic lesions; inspect sinuses and mastoid air cells for fractures or opacity that may suggest fluid, pus, blood, or tumour; status of the orbital floor in cases of facial trauma (coronal series best)
- dura and subdural space: crescent-shaped hyperdensity in the subdural space suggests subdural hematoma; lentiform hyperdensity in the epidural space suggests epidural hematoma; check symmetry of dural thickness, where increased thickness may suggest the presence of blood
- parenchyma: asymmetry of the parenchyma suggests midline shift; poor contrast between grey and white matter suggests possible infarction, tumour, edema, infection, or contusion; hyperdensity in the parenchyma suggests enchancing lesions, intracerebral hemorrhage, or calcification; central grey matter nuclei (e.g. globus pallidus, putamen, internal capsule) should be visible, otherwise, suspect infarct, tumour, or infection
- ventricles/sulci/cisterns: examine position of ventricles for evidence of midline compression/shift; hyperdensities in the ventricles suggest ventricular/subdural hemorrhage; enlarged ventricles suggest hydrocephalus; obliteration of sulci may suggest presence of edema causing effacement, possible blood filling in the sulci, or tumour; cistern hyperdensities may suggest blood, pus, or tumour
- please refer to Toronto Notes website for supplementary material on how to approach a head CT



**Figure 34. Insular ribbon sign (left side)** Hypodensity of insular cortex representing early sign of infarction

# Selected Pathology

- see Neurosurgery, NS4 for intracranial mass lesions
- see Neurosurgery, NS31 for head trauma and Plastic Surgery, PL31 for craniofacial injuries
- see Emergency Medicine, ER9 for spinal trauma
- see Neurosurgery, NS24 and Orthopedic Surgery, OR23 for degenerative spinal abnormalities

## Cerebrovascular Disease (Neurosurgery, NS18)

- pathogenesis of stroke: see Neurosurgery, NS18
- best imaging modality: infarcts best detected by MRI > CT

**DDx for Ring Enhancing Cerebral Lesion**

**MAGIC DR**
**M**etastasis
**A**bscess
**G**lioblastoma multiforme
**I**nfarction (subacute/chronic)
**C**ontusion/hematoma
**D**emyelinating disease (e.g. MS)
**R**adiation necrosis

**Table 17. Temporal Findings of Infarction with CT and MRI**

| Time from Stroke Onset | CT | MRI |
|---|---|---|
| **Hyperacute (0-24 h)** | Usually normal within 6 h<br>Edema (loss of grey-white matter differentiation – "insular ribbon sign", effacement of sulci, mass effect)<br>Hyperattenuating artery "hyperdense MCA sign" repre-senting intravascular thrombus/emboli may be seen in ischemic stroke<br>Hyperattenuating acute blood surrounded by edema may be seen in hemorrhagic stroke | Hyperintensity on DWI within minutes of arterial occlusion due to restriction of water movement indicative of cytotoxic edema<br>Hypointensity on ADC within minutes<br>Hyperintensity on T2/FLAIR approximately 6 h after onset due to edema (loss of grey-white matter differentiation, effacement of sulci, mass effect) |
| **Acute (24 h-1 wk)** | Increasing edema (seen as hypoattenuation) may result in significant positive mass effect | Continued hyperintensity on DWI<br>Hypointensity on ADC reaches nadir at 3-5 d and begins to increase<br>Continued hyperintensity on T2/FLAIR |
| **Subacute (1-3 wk)** | Resolution of edema leads to increased attenuation of infarcted area that may regain near-normal density and mask stroke "fogging phenomenon" | Continued hyperintensity on DWI due to "T2 shine through"<br>Intensity on ADC continues to rise, pseudo-normalizes at 10-15 d, and then surpasses that of surrounding normal tissue<br>Continued hyperintensity on T2/FLAIR |
| **Chronic (>3 wk)** | Encephalomalacia (parenchymal volume loss) appears as hypoattenuation with negative mass effect | Hyperintensity on DWI/T2/FLAIR progressively decreases<br>ADC intensity remains elevated |

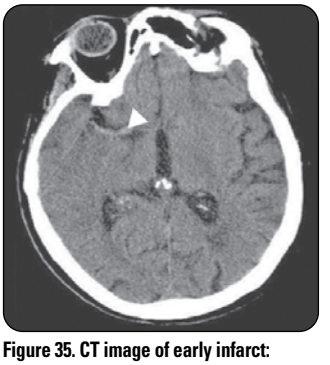


**Figure 35. CT image of early infarct: hyperdense artery**

- carotid artery disease
  - best imaging modality: Duplex (Doppler U/S)
  - other modalities: MRA or CTA if carotid angioplasty or endarterectomy is under consideration (conventional angiography reserved for inadequate MRA or CTA)

## Multiple Sclerosis (see Neurology, N52)

- best imaging modality: MRI has high sensitivity in diagnosing MS (>90%) but low specificity (71-74%)
- findings
  - characteristic lesion on MRI is cerebral or spinal plaque
  - plaques typically found in periventricular region, corpus callosum (arranged at right angles to the corpus callosum), centrum semiovale, and to a lesser extent in deep white matter structures and basal ganglia
  - "Dawson's fingers" refers to perivenular regions of demyelination that are seen to radiate outwards into the deep periventricular region
  - plaques usually have ovoid appearance, hyperintense on T2 and hypointense on T1
  - conventional T2 may underestimate plaque size and overall plaque burden – advanced techniques (diffusion tensor imaging and MR spectroscopy) can be of use
  - perivascular and interstitial edema may be prominent



**Figure 36. DWI of patient with right frontotemporal infarct**

- spinal cord lesions typical of MS
  - little or no cord swelling
  - unequivocal hyperintensity on T2-weighted sequences
  - size at least 3 mm but less than 2 vertebral segments in length
  - occupy only part of the cord in cross-section
  - focal (i.e. clearly delineated and circumscribed on T2-weighted sequences)

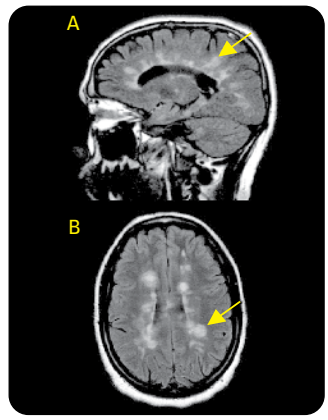



**Figure 37. T2-weighted FLAIR: (A) sagittal (B) axial images of multiple sclerosis with periventricular "Dawson's Fingers"**

### CNS Infections

- **meningitis**
  - pathogenesis: inflammation of the pia or arachnoid mater, most often secondary to hematogenous spread from infection or via organisms gaining access across areas not protected by the blood-brain barrier (choroid plexus or circumventricular organs)
  - pathogens include: *S. pneumoniae, H. influenzae, N. meningitidis, L. monocytogenes*
    - best imaging modality: MRI (T2-weighted/FLAIR)
    - findings
      - meningeal enhancement (following the gyri/sulci and/or basal cisterns), hydrocephalus (communicating), cerebral swelling, subdural effusion
  - a normal MRI does not rule out leptomeningitis
- **herpes simplex encephalitis** (see Infectious Diseases, ID17)
  - pathogenesis: inflammation of the brain parenchyma secondary to infection with herpes simplex virus, asymmetrically affects the limbic regions of the brain (i.e. temporal lobes, orbitofrontal region, insula, and cingulate gyrus)
  - best imaging modality: MRI (T1- and T2-weighted)
  - findings
    - acute (within 4-5 d): asymmetric high intensity lesions on T2 MRI in temporal and inferior frontal lobes strongly suggestive
    - DDx: infarct, tumour, status epilepticus, limbic encephalitis
    - CT may show low density in temporal lobe and insula; rarely basal ganglia involvement
    - long-term may show parenchymal loss to affected areas
- **cerebritis/cerebral abscess**
  - pathogenesis: an infection of the brain parenchyma (cerebritis) which can progress to a collection of pus (abscess), most frequently due to hematogenous spread of infectious organisms, commonly located in the distribution of the MCA
  - pathogens include: S. aureus (often in IV drug users, nosocomial), Streptococcus, Gram negative bacteria, Bacteroides
  - best imaging modality: MRI including DWI imaging series (abscess will be DWI positive); CT still used as a viable alternative
  - findings according to one of four stages of abscess formation
    - early cerebritis (1-3 d): inflammatory infiltrate with necrotic centre, low intensity on T1, high intensity on T2
    - late cerebritis (4-9 d): ring enhancement may be present
    - early capsule (10-13 d): ring enhancement
    - late capsule (14 d or greater): well demarcated ring-enhancing lesion, low intensity core, with mass effect; considerable edema around the lesion, seen as hyperintensity on T2

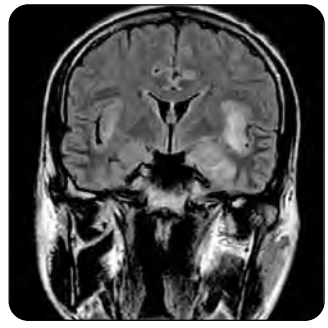


**Figure 38. T2-weighted (FLAIR) coronal image of herpes simplex virus encephalitis affecting temporal lobes**

# Musculoskeletal System

## Modalities

- see *Imaging Modalities*, MI2 for advantages and disadvantages of the following:

### Plain Film/X-Ray

- usually initial study used in evaluation of bone and joint disorders
- indications: fractures and dislocations, arthritis, assessment of malunion or nonunion, orthopedic hardware, and bone lesions (initial)
- minimum of two orthogonal views (usually AP and lateral) to rule out a fracture
- image proximal and distal joints, particularly important with paired bones (e.g. radius/ulna)
- minimally effective in evaluating soft tissue injury

### CT

- evaluation of fine bony detail
- indications: assessment of complex, comminuted, intra-articular, or occult fractures including distal radius, scaphoid, skull, spine, acetabulum, calcaneus, and sacrum
- evaluation of soft tissue calcification/ossification

### MRI

- indications: evaluation of internal derangement of joints (e.g. ligaments, joint capsule, menisci, labrum, cartilage), assessment of tendons and muscle injuries, characterization and staging of soft tissue and bony masses, infection of bone (osteomyelitis)

### Ultrasound
- indications: tendon injury (e.g. rotator cuff, Achilles tendon), detection of soft tissue masses and to determine whether cystic or solid, detection of foreign bodies, U/S-guided biopsy and injections, bone/joint evaluation pre-ossification (e.g. DDH in early months)
- Doppler determines vascularity of structures

### Nuclear Medicine (Bone Scintigraphy)
- determine the location and extent of bony lesions
- $^{99m}$Tc-methylene diphosphonate localizes to areas of increased bone turnover or calcification – growth plate in children, tumours, infections, fractures, metabolic bone disease (e.g. Paget's), sites of reactive bone formation, and periostitis
- advantages: very sensitive, capable of imaging entire body with relatively low dose radiation
- disadvantages: low specificity, not widely available due to special requirements (e.g. gamma camera, radiopharmaceuticals)

## Approach to Bone X-Rays

- identification: name, MRN, age of patient, type of study, region of investigation
- soft tissues: swelling, calcification/ossification
- joints: alignment, joint space, presence of effusion, osteophytes, erosions, bone density, overall pattern, and symmetry of affected joint
- bone: periosteum, cortex, medulla, trabeculae, density, articular surfaces, bone destruction, bone production, appearance of the edges, or borders of any lesions



**Figure 39. X-ray findings of first carpometacarpal joint:** normal image (left) and osteoarthritis (right) with joint space narrowing and subchondral sclerosis

## Trauma

### Fracture/Dislocation
- description of fractures
- site of fracture (bone, region of bone, intra-articular vs. extra-articular)
- pattern of fracture line (simple vs. comminuted)
- displacement (distal fragment with reference to the proximal fragment)
- soft tissue involvement (calcification, gas, foreign bodies)
- type of fracture (stress vs. pathologic)
- for specific fracture descriptions and characteristics of fractures, see Orthopedics, OR5

## Arthritis

### Radiographic Hallmarks of Osteoarthritis
- joint space narrowing – typically non-uniform
- subchondral sclerosis
- subchondral cyst formation
- osteophytes

### Radiographic Hallmarks of Rheumatoid Arthritis
- joint space narrowing – typically uniform
- soft tissue swelling
- erosions
- periarticular osteopenia

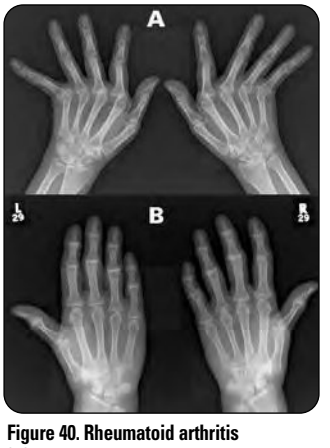



**Figure 40. Rheumatoid arthritis (A) compared with osteoarthritis (B) X-ray findings**

## Bone Tumour

### Approach
- metastatic tumours to bone are much more common than primary bone tumours, particularly if age >40 yr
  - diagnosis usually requires a biopsy if primary not located
  - few benign tumours/lesions have potential for malignant transformation
  - MRI is good for tissue delineation and pre-operative assessment of surrounding soft tissues, neurovascular structures, and medullary/marrow involvement
  - plain film is less sensitive than other modalities but useful for assessing aggressiveness and constructing differential diagnosis

### Considerations and Tumour Characteristics
- for specific bone tumours, see Orthopedic Surgery, OR46
- age: most common tumours by age group
  - <1 yr of age: metastatic neuroblastoma
  - 1-20 yr of age: Ewing's sarcoma in tubular bones
  - 10-30 yr of age: osteosarcoma and Ewing's tumour in flat bones
  - >40 yr of age: metastases, multiple myeloma, and chondrosarcoma
- multiplicity: metastases, myeloma, lymphoma, fibrous dysplasia, enchondromatosis
- location within bone
  - epiphysis: giant cell tumour, chondroblastoma, geode, eosinophilic granuloma, infection
  - metaphysis: simple bone cyst, aneurysmal bone cyst, enchondroma, chondromyxoid fibroma, nonossifying fibroma, osteosarcoma, chondrosarcoma
  - diaphysis: fibrous dysplasia, aneurysmal bone cyst, brown tumours, eosinophilic granuloma, Ewing's sarcoma

- expansile
  - aneurysmal bone cyst, giant cell tumour, enchondromas, brown tumours, metastases (especially renal and thyroid), plasmacytoma
- matrix mineralization
  - chondroid (popcorn calcification) or osseous
- margin/zone of transition: area between lesion and normal bone
- cortex: intact, disturbed
- periosteal reaction: onion-skinning, sunburst, Codman's triangle, periosteal neocortex
- soft tissue mass

**Benign Lesions which may have Aggressive Features**
- Osteomyelitis
- Osteoblastoma
- Aneurysmal bone cyst
- Langerhans cell histiocytosis
- Myositis ossificans

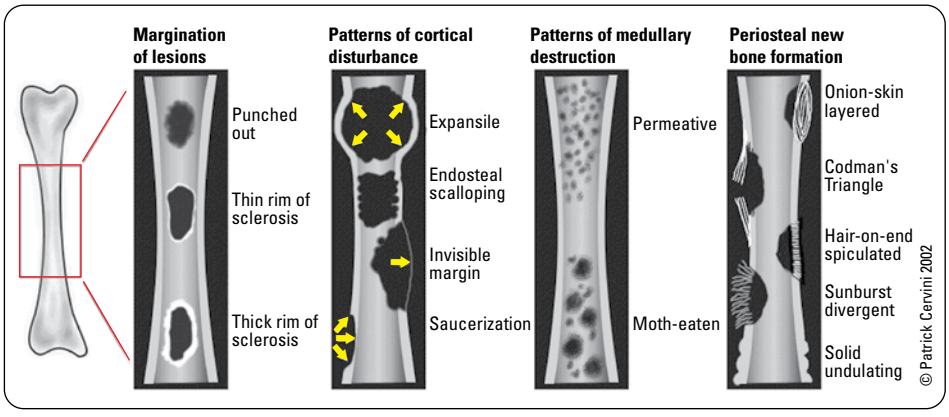



**Figure 41. Radiographic appearance of bone remodelling and destruction processes**

**Periosteal Reaction**
- "Onion skinning" = Ewing's sarcoma
- "Sunburst", "hair on end" = osteosarcoma
- "Codman's triangle" = osteosarcoma, Ewing's sarcoma, subperiosteal abscess

**Table 18. Characteristics of Benign and Malignant Bone Lesions**

| Benign | Malignant |
|---|---|
| Thin sclerotic margin/sharp delineation of lesion | Poor delineation of lesion – wide zone of transition |
| Overlying cortex intact | Loss of overlying cortex/bony destruction |
| No or simple periosteal reaction | Periosteal reaction |
| No invasion of surrounding soft tissue | Invasion of surrounding soft tissue |

## Metastatic Bone Tumours

Lytic = decreased density
Sclerotic = increased density

- all malignancies have potential to metastasize to bone
- metastases are 20-30x more common than primary bone tumours
- metastasis can cause a lytic or a sclerotic reaction when seeding to bone
- when a primary malignancy is first detected, a bone scan is often part of the initial workup
- may present with pathological fractures or pain
- biopsy or determination of primary is the only way to confirm the diagnosis
- most common metastatic bone tumours: breast, prostate, lung, see Orthopedic Surgery, OR46

**"KLM flies to periphery"**

**K**idney
**L**ung
**M**elanoma

**Table 19. Characteristic Bone Metastases of Common Cancers**

| Lytic | Sclerotic | Expansile | Peripheral |
|---|---|---|---|
| Breast | Prostate | Thyroid | Kidney |
| Lung | Breast | Renal | Lung |
| Thyroid | Lymphoma | | Melanoma |
| Kidney | Lung | | (KLM: flies to the periphery) |
| Multiple myeloma | Bowel | | |
| | Medulloblastoma | | |
| | Treated tumours | | |

# Infection

## Osteomyelitis

- MRI is the imaging modality of choice for demonstrating bone, bone marrow, and soft tissue abnormalities
- $^{99m}$Tc, followed by $^{111}$In-labeled white cell scan or gallium radioisotope scan
- plain film changes visible 8-10 d after process has begun
  - soft tissue swelling
  - local periosteal reaction
  - pockets of air (from anaerobes) may be seen in the tissues, may also suggest necrotizing fasciitis
  - mottled and nonhomogeneous with a classic "moth-eaten" appearance
  - endosteal scalloping
  - cortical destruction
  - peripheral sclerosis (late sign)

### Bone Abscess
- overlying cortex has periosteal new bone formation
- sharply outlined radiolucent area with variable thickness in zone of transition
- variable thickness periosteal sclerosis
- sequestrum: a piece of dead bone within a Brodie's abscess (rare form of osteomyelitis on bone metaphyses)
- a sinus tract or cloaca may communicate between the abscess through the cortex to the surface of the bone
- best imaging modality: MRI for bone, bone marrow, and soft tissue abnormalities; CT for sequestra and cortical erosions

## Metabolic Bone Disease

### Osteoporosis
- reduction in amount of normal bone mass; fewer and thinner trabeculae; diffuse process affecting all bones
- DEXA: gold standard for measuring bone mineral density
  - T-score: the number of standard deviations from the young adult mean, most clinically valuable
    - osteopenia: –2.5< T-score <–1
    - osteoporosis: T-score ≤–2.5
  - Z-score: the number of standard deviations from the age-matched mean, helpful in diagnosing secondary osteoporosis
  - risk of fracture: related to bone mineral density, age, history of previous fractures, steroid therapy
  - diagnostic sensitivity of DEXA highest when bone mineral density measured at lumbar spine and proximal femur
- appearance on plain film (not sensitive; changes detectible only after large reduction in bone mineral density)
  - osteopenia: reduced bone density on plain films
    - may also be seen with osteomalacia, hyperparathyroidism, and disuse
  - compression of vertebral bodies
  - "codfish vertebra" (biconcave vertebral bodies), "picture frame vertebra" (cortical loss), "ghost vertebra" (trabecular loss)
  - long bones have appearance of thinned cortex and increased medullary cavity
    - look for complications of osteoporosis (e.g. insufficiency fractures: hip, vertebrae, sacrum, pubic rami)
- see Endocrinology, E43

**Osteoporosis**
Reduced amount of bone

**OsteoMalacia**
Normal amount of bone, but reduced **M**ineralization of normal osteoid

### Osteomalacia/Rickets
- reduction in bone mineral density; normal amount of bone, but reduced mineralization of normal osteoid
- usually due to vitamin D deficiency, resulting in softening and bowing of long bones
- similar to osteoporosis, initial radiological appearance of osteopenia (coarse and poorly defined bone texture)
- "fuzzy", ill-defined trabeculae
- insufficiency fractures
- Looser's zones (pseudofracture)
  - characteristic radiologic feature
  - fissures or clefts at right angles to long bones and extending through cortex
  - DDx: chronic renal disease, fibrous dysplasia, hyperthyroidism, Paget's, osteodystrophy, X-linked hypophosphatemia

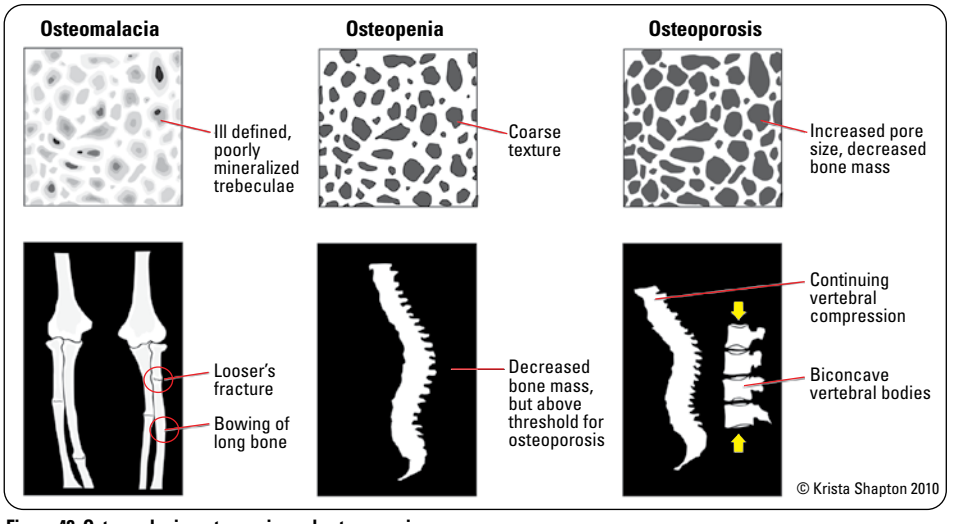



**Figure 42. Osteomalacia, osteopenia, and osteoporosis**

### Hyperparathyroidism
- most common cause is renal failure (secondary hyperparathyroidism)
- chondrocalcinosis is a common complication
- calcium crystal deposition in hyaline cartilage or fibrocartilage (including arteries and peri-articular soft tissue)
- resorption of bone typically in hands (subperiosteal and at tufts), sacroiliac joints (subchondral), skull ("salt and pepper" appearance), subligamentous resorption (ischial tuberosity, trochanters, and clavicle), osteoclastoma (brown tumours)
- "rugger jersey spine": band-like osteosclerosis at superior/inferior margins of vertebral bodies

### Paget's Disease
- abnormal remodelling involving single or multiple bones – especially skull, spine, pelvis
- 3 phases: 1st phase = lytic, 2nd phase = mixed (lytic/sclerotic), 3rd phase = sclerotic
- coarsening of the trabeculae with bone expansion
- bone softening/bowing
- bone scan will reveal high activity
- thickened cortex
- see Endocrinology, E46

# Nuclear Medicine

## Brain

- $^{99m}$Tc-exametazime (HMPAO) and $^{99m}$Tc-bicisate (ECD) imaging used in SPECT to assess cerebral blood flow and cellular metabolism, taken up predominantly in grey matter
  - used for dementia, traumatic brain injury, and to a lesser extent vasculitis, neuropsychiatric disorders, and occasionally stroke
  - most commonly used tracers to confirm brain death (i.e. absent blood flow to the brain and absent uptake on delayed planar and SPECT images in brain and brainstem, assuming study is technically adequate)
  - either tracer can be used for seizure imaging to assess for the most likely location of epileptogenic focus, but usually must be made available for 24 h and the patient followed by a nurse who is competent to administer the activity at the time of seizure
- PET imaging assesses metabolic activity most commonly with $^{18}$FDG; used for dementia imaging, grading and staging of brain tumours, occasionally for seizure disorder imaging, and vasculitis; PET imaging with amyloid tracers for diagnosis of Alzheimer's disease is becoming more common
- CSF imaging, intrathecal administration of $^{111}$In DTPA to evaluate CSF leak or to differentiate normal pressure hydrocephalus from brain atrophy
- CSF shunt evaluation for obstruction (most commonly ventriculoperitoneal) with sterile or pyrogen free $^{99m}$Tc (usually) or $^{111}$In-DTPA; small quantity of activity is injected into the reservoir under sterile conditions and should flow freely into the peritoneal cavity by 45 min; maneuvers such as pumping the shunt, sitting the patient upright or ambulating are acceptable to encourage flow during this time
- adrenergic imaging of the heart with MIBG has been used to differentiate dementias with autonomic dysfunction (i.e. Lewy Body and Parkinson's disease) from other forms of dementia (i.e. autonomic impairment associated with decreased MIBG activity in the heart)

## Thyroid

### Radioactive Iodine Uptake (see Endocrinology, E23)
- index of thyroid function (trapping and organification of iodine)
- radioactive $^{123}$I given PO to fasting patient (small quantity)
- measure percentage of administered iodine taken up by thyroid
- increased RAIU: toxic multinodular goitre, toxic adenoma, Graves' disease
- decreased RAIU: subacute thyroiditis, late Hashimoto's disease, exogenous thyroid hormone or iodine, falsely decreased in patient with recent radiographic contrast studies, high dietary iodine (e.g. seaweed, taking a "thyroid vitamin")
- important – iodine uptake helps in the differential of hyperthyroidism only, not hypothyroidism (exception is pediatrics)

### Thyroid Imaging (Scintiscan)
- $^{99m}$Tc-pertechnetate IV or radioactive iodine ($^{123}$I); most Canadian sites use pertechnetate to reduce cost
- provides functional anatomic detail
- hot (hyperfunctioning) lesions: usually benign (e.g. adenoma, toxic multinodular goitre), cancer unlikely (<1%) – No FNA
- cold (hypofunctioning) lesions: cancer must be considered until biopsy negative even though only 6-10% are cancerous; decision to biopsy should be based on clinical and sonographic features
- isointense i.e. "warm" lesions: cancer must be considered as an isointense lesion may represent cold nodules superimposed on normal tissue; if cyst suspected, correlate with U/S

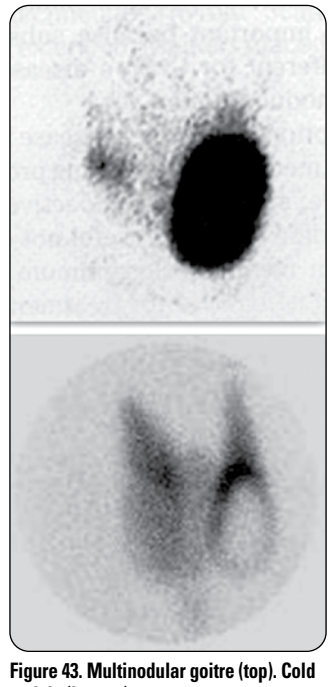


**Figure 43. Multinodular goitre (top). Cold nodule (bottom)**

### Radioiodine Ablation
- $^{131}I$ for Graves' disease, multinodular goitre, thyroid cancer (in the case of thyroid cancer, ablation performed at higher dose and after thyroidectomy)
- serum thyroglobulin used to detect recurrent thyroid cancer in a patient who has received ablation
- advice should be given for patient-specific precautions to remain away from family members and caregivers to reduce radiation exposure after thyroid ablation, do not initiate pregnancy for 6 mo, small risk of exophthalmos, thyroid storm, secondary malignancy

### Pediatric Hypothyroidism
- pertechnetate thyroid scan can differentiate thyroid agenesis, hemiagenesis, lingular thyroid, organification defect, however should not wait for a diagnosis to start thyroid hormone replacement in a neonate; start immediately

## Respiratory

### V/Q Scan
- evaluate areas of lung in which there is a ventilation/perfusion mismatch
- ventilation scan – assess air flow within lungs
  - patient breathes radioactive gas (nebulized $^{99m}Tc$-DTPA, $^{133}Xe$, or most commonly Technegas) through a closed system, filling alveoli proportionally to ventilation
  - ventilation scan defects indicate: airway obstruction (i.e. air trapping), chronic lung disease, bronchospasm, tumour mass obstruction
- perfusion scan – assess blood circulation within lungs
  - radiotracer injected IV ($^{99m}Tc$-MAA) → trapped in pulmonary capillaries (0.1% of arterioles occluded) according to blood flow
  - relatively contraindicated in severe pulmonary HTN, right-to-left shunt, previous history of pneumonectomy, small child. In these cases fewer particles are usually given
- to rule out PE
  - indications: some institutions favour in pregnancy (lower radiation dose to breast than CT), or where CT contrast contraindicated (e.g. contrast allergy, renal failure)
  - areas of lung that are well-ventilated but not perfused (unmatched defect) are suspicious for acute infarction
  - defects are wedge-shaped, extend to periphery, usually bilateral and multiple
  - often reported as high probability (>2 large i.e. segmental mismatched perfusion defects), intermediate, low, very low, or normal according to modified PIOPED II criteria, although are increasingly reported as PE present, indeterminate or normal
  - useful in finding clinically important emboli
  - decreased detection of incidentalomas commonly found on CT
- not valid for assessment of PE when patients have consolidation and the test can be limited by ventilatory problems (e.g. COPD), much like CT
- modified V/Q scan (perfusion only, lower dose contrast) may be used for pregnant patients if CXR is normal or if there are ventilatory problems



**Ventilation Scan Defects Indicate…**
ABC Tumour
Airway obstruction
Bronchospasm
Chronic lung disease
Tumour mass obstruction



**Perfusion Scan Defects Indicate…**
Reduced blood flow due to PE
COPD
Asthma
Bronchogenic carcinoma
Inflammatory lung diseases (pneumonia, sarcoidosis)
Mediastinitis
Mucous plug
Vasculitis



**V/Q Scan**
For PE investigation: normal scan makes PE unlikely
Probability of PE: high 80-100%, intermediate 20-80%, low <20%, very low <10%

## Cardiac

### Myocardial Perfusion Scanning
- to investigate coronary artery disease (CAD), assess treatment of CAD, pre-op risk stratification, viability testing
- $^{99m}Tc$-sestamibi, or $^{99m}Tc$-tetrofosmin are used most commonly, thallium 201 was used previously but largely discontinued due to high radiation doses to patients and unfavourable imaging characteristics; today thallium still used for viability studies
- injected at peak exercise (85% max predicted heart rate by the Bruce protocol, chest pain, ECG changes), after persantine challenge (vasodilator), or after dobutamine infusion (chronotropic, again to 85% predicted heart rate); can be done as stress only protocol with optional rest or as stress and rest combined protocol (i.e. as 1 d or 2 d protocol)
- patients with left bundle branch block usually given pharmacologic stress because ECG is difficult to interpret for ST changes and avoids a characteristic artifact
- pharmacologic stress contraindicated if sBP is <90; persantine exacerbates asthma, so patients with asthma and wheeze who cannot exercise usually get dobutamine infusion; reverse persantine with aminophylline or caffeine
- persistent defect (present at rest and stress) suggests infarction or myocardial scar; reversible defect (only present during stress) suggests ischemia
- used to discriminate between reversible (ischemia) vs. irreversible (infarction) changes when other investigations are equivocal
- COURAGE trial indicates that patients with >10% ischemic myocardium benefit most from revascularization
- see Cardiology and Cardiac Surgery, C13

### Radionuclide Ventriculography
- $^{99m}$Tc-tagged to red blood cells, tagged albumin is also acceptable
- first pass through RV → pulmonary circulation → LV; provides information about RV function, presence of shunts
- cardiac MUGA scan sums multiple cardiac cycles, usually at least 200 beats
- evaluation of LV function and regional wall motion, ejection fraction
- images are obtained by gating (synchronizing) the count acquisitions to the ECG signal
- can assess diastolic dysfunction
- provides information on ejection fraction (normal = 50-65%), ventricular volume, and wall motion
- indications: most commonly to monitor potential cardiac toxicity with chemotherapy or herceptin, as a gold standard of ejection fraction in defibrillator workup

## Abdomen and Genitourinary System

### HIDA Scan (Cholescintigraphy)
- IV injection of $^{99m}$Tc-disofenin (DISIDA) or $^{99m}$Tc-mebrofenin which is bound to protein, taken up, and excreted by hepatocytes into biliary system
- can be performed in non-fasting state but prefer NPO after midnight
- indicated in workup of cholecystitis when abdominal ultrasound result is equivocal:
  - acute cholecystitis: no visualization of gallbladder at 4 h or 1 h after administration of morphine
  - chronic cholecystitis: no visualization of gallbladder at 1 h but seen at 4 h or after morphine administration
- gallbladder visualized when cystic duct is patent (rules out acute cholecystitis with >99% certainty), usually seen by 30 min-1 h
- differential diagnosis of obstructed cystic duct: acute/chronic cholecystitis, decreased hepatobiliary function (commonly due to alcoholism), bile duct obstruction, parenteral nutrition, fasting less than 4 h or more than 24 h
- also used to assess bile leaks post-operatively or in trauma
- gallbladder ejection fraction (>38% is normal) can be measured after a fatty meal or cholecystokinin to assess for biliary dyskinesia

### RBC Scan
- IV injection of radiotracer with sequential images of the abdomen ($^{99m}$Tc RBCs)
- GI bleed
  - if bleeding acutely at <0.5 mL/min, the focus of activity in the images generally indicates the site of the acute bleed, look for a change in shape and location on sequential image, requires active bleeding to localize (more sensitive than angiography in detecting slower bleeding)
  - if bleeding acutely at >0.5 mL/min, use angiography (more specific, better for localizing, both diagnostic and therapeutic)
- liver lesion evaluation
  - hemangioma has characteristic appearance: cold early (limited blood flow to lesion), fills in later (accumulation of tagged cells greater than surrounding liver parenchyma)

### Other Important Nuclear Medicine Abdominal Tests
- Meckel's Scan: uses $^{99m}$Tc pertechnetate; give patient ranitidine premedication; Meckel's diverticulum contains gastric mucosa which will light up at the same time as the stomach and get brighter with time like stomach
- $^{111}$In octreoscan: a somatostatin analog used for evaluation and staging of neuroendocrine tumours including carcinoid; gastrinoma and carcinoid tend to be more octreotide avid than insulinoma
- iodinated MIBG: a norepinephrine analogue, used for pheochromocytoma, neuroblastoma and medullary thyroid cancer most commonly; limited cardiac applications as above
- solid and liquid gastric emptying: a standardized solid or liquid meal is labelled, usually with $^{99m}$Tc sulfur colloid and gastric emptying studied over time. There are normal ranges for solids and liquids

### Urea Breath Test
- indication: diagnosis of gastric *H. pylori* infection
- patient administered 14C-labelled urea orally, urea metabolized by *H. pylori* to ammonia and $14CO_2$, 14C-labled $CO_2$ is measured via plastic filament detectors or liquid scintillation

### Functional Renal Imaging
- evaluation of renal function and anatomy using $^{99m}$Tc DTPA or $^{99m}$Tc MAG3
- frequently used to provide index of relative function between two kidneys
- frequently used in adults to assess for UPJ obstruction (by assessing the clearance half time with furosemide), and assess renal transplants or as a nuclear GFR study in patients wanting to donate kidneys
- in children, imaging with $^{99m}$Tc DMSA is used to assess for pyelonephritis
- in children, the injection of tracer into the bladder via foley catheter is often used to assess for reflux

# Bone

### Bone Scan
- isotopes, usually $^{99m}$Tc-diphosphonate
- radioactive tracer binds to hydroxyapatite of bone matrix
- increased binding when increased blood supply to bone and/or high bone turnover (active osteoblasts)
- indications: bone pain of unknown origin, staging or restaging of cancer with boney mets (or primary bone cancer), imaging of arthroplasty complications like loosening or infection, osteomyelitis imaging
- when used to assess for osteomyelitis, usually done in combination with gallium or white blood cell scan
- differential diagnosis of positive bone scan: bone metastases (primary breast, prostate, lung, thyroid), primary bone tumour, arthritis, fracture, infection, anemia, Paget's disease
- lytic lesions like multiple myeloma, renal cell cancer, eosinophilic granuloma: typically normal or cold (false negative); need a skeletal survey
- "superscan": increased bone uptake and poor renal uptake due to diffuse metastases (primary breast, prostate) or metabolic causes (e.g. renal osteodystrophy)

# Interventional Radiology

## Vascular Procedures

### Angiography
- injection of contrast material through a catheter placed directly into an artery or vein to delineate vascular anatomy
- catheter can be placed into a large vessel (e.g. aorta, vena cava) for a "flush" or selectively placed into a branch vessel for more detailed examination of smaller vessels and specific organs
- often used in the operating room to provide fluoroscopic guidance for exposure of diseased vessel
- indications: diagnosis of primary occlusive or stenotic vascular disease, aneurysms, coronary, carotid and cerebral vascular disease, PE, trauma, bleeding (GI, hemoptysis, hematuria), vascular malformations, as part of endovascular procedures (endovascular aneurysm repair, thrombolysis, stenting, and angioplasties)
- complications (<5% of patients): puncture site hematoma, infection, pseudoaneurysm, AV fistula, dissection, thrombosis, embolic occlusion of a distal vessel
- due to improved technology, non-invasive evaluation of vascular structures is being performed more frequently (colour Doppler U/S, CTA, and MRA)
- see *Neuroradiology*, MI18

Advanced ischemia patients should receive surgery rather than thrombolysis

### Percutaneous Transluminal Angioplasty and Stents
- introduction and inflation of a balloon into a stenosed or occluded vessel to restore distal blood supply
- common alternative to surgical bypass grafting with 5 yr patency rates similar to surgery, depending on site
- renal, iliac, femoral, mesenteric, subclavian, coronary, and carotid artery stenoses are amenable to treatment
- vascular stents may help improve long-term results by keeping the vessel wall patent after angioplasty; also used for angioplasty failure or complications
- stent grafts (metal mesh covered with durable fabric) may provide an alternative treatment option for aneurysms and AV fistulas
- complications: similar to angiography, but also includes vessel rupture

Chemoembolization delivers chemotherapy directly into the tumour through its feeding blood supply and traps the drug in place by embolization

### Thrombolytic Therapy
- may be systemic (IV) or catheter directed
- infusion of a fibrinolytic agent (urokinase, streptokinase, TNK, tPA – used most commonly) via a catheter inserted directly into a thrombus
- can restore blood flow in a vessel obstructed with a thrombus or embolus
- indications: treatment of ischemic limb (most common indication), early treatment of MI or stroke to reduce organ damage, treatment of venous thrombosis (DVT or PE)
- complications: bleeding, stroke, distal embolus, reperfusion injury in delayed intervention with myoglobinuria and renal failure if advanced ischemia present

**Thrombolytic Therapy for Pulmonary Embolism**
Cochrane Database Syst Rev 2015;9:CD004437
**Purpose**: To assess the effects of thrombolytic therapy in patients with acute pulmonary embolism (PE).
**Methods**: Systematic review of RCTs evaluating thrombolytic therapy followed by heparin versus heparin alone, heparin plus placebo or surgical intervention in patients with acute PE. Studies comparing two different thrombolytic agents or different doses of the same thrombolytic drug were not considered eligible. Main outcomes of interest were death, recurrence of PE, and major and minor hemorrhagic events.
**Results**: Eighteen trials with2197 participants were included. Thrombolytics plus heparin were associated with a reduction in odds of death relative to heparin alone or heparin plus (OR 0.57, 95% CI 0.37 to 0.87, P = 0.02) and recurrence of PE (OR 0.51; 0.29 to 0.89, P = 0.02). Incidence of major and minor hemorrhagic events was statistically significantly higher in the thrombolytics group than the control group (OR 2.90, 95% CI 1.95 to 4.31, P <0.001). Length of hospital stay (mean difference (MD) -1.35, -4.27 to 1.58) and quality of life were similar between groups. Based on one study, stroke occurred more often in the thrombolytics group (OR 12.10, 1.57 to 93.39).
**Conclusion**: Low-quality evidence suggests thrombolytics reduce death following acute PE compared with heparin and may be helpful in reducing PE recurrence, but may cause more major and minor hemorrhagic events and stroke events.

### Embolization
- injection of occluding material into vessels
- permanent agents: amplatzer plugs, coils, glue, and onyx
- temporary: gel foam, autologous blood clots
- indications: management of hemorrhage (epistaxis, trauma, GI bleed, GU bleed), treatment of arteriovenous malformation, pre-operative treatment of vascular tumours (bone metastases, renal cell carcinoma), varicocele embolization for infertility, symptomatic uterine fibroids
- complications: post-embolization syndrome (pain, fever, leukocytosis), unintentional embolization of a non-target organ with resultant ischemia

### Inferior Vena Cava Filter
- insertion of temporary or permanent metallic "umbrellas" to mechanically trap emboli and prevent PE
- inserted via femoral vein, jugular vein, or antecubital vein
- usually placed infrarenally to avoid renal vein thrombosis
- indications: contraindication to anticoagulation, failure of adequate anticoagulation (e.g. recurrent PE despite therapeutic anticoagulant levels), complication of anticoagulation



**Figure 44. Retrievable IVC filter**

### Central Venous Access
- variety of devices available
- PICC, external tunneled catheter (Hickman or dialysis catheters), subcutaneous port (Portacath®)
- indications: chemotherapy, TPN, long-term antibiotics, administration of fluids and blood products, blood sampling
- complications: venous thrombosis, central venous stenosis, infection including sepsis, and pneumothorax

**Indications for Central Venous Access**

**FAT CAB**
**F**luids
**A**ntibiotics
**T**PN
**C**hemotherapy
**A**dministration of blood
**B**lood sampling

## Nonvascular Interventions

### Percutaneous Biopsy
- alternative to open surgical procedure
- many sites are amenable to biopsy using U/S, fluoroscopy, CT or MR guidance
- complications: false negative (sampling error or tissue necrosis), needle tract seeding, hemorrhage (particularly for splenic biopsies), pneumothorax in 30% of lung biopsies (chest tube required in ~5%), acute pancreatitis (pancreatic biopsies), bleeding from liver biopsies in patients with uncorrectable coagulopathies or ascites (can be minimized with transjugular approach)

### Abscess Drainage
- placement of a drainage catheter into an infected fluid collection
- administer broad spectrum IV antibiotics prior to procedure
- routes: percutaneous (most common), transgluteal, transvaginal, transrectal
- complications: hemorrhage, injury to intervening and nearby structures (e.g. bowel), bacteremia, sepsis, failure to access

### Percutaneous Biliary Drainage/Cholecystostomy
- placement of drainage catheter ± metallic stent into obstructed biliary system (PBD) or gallbladder (cholecystostomy) for relief of jaundice or infection
- percutaneous gallbladder access can be used to crush or remove stones
- indications
  - cholecystostomy: acute cholecystitis
  - PBD: biliary obstruction secondary to stone or tumour, cholangitis, acute biliary pancreatitis
- complications
  - acute: sepsis, hemorrhage
  - long-term: tumour ingrowth and stent occlusion


**Figure 45. Femoral arteriogram: distal occlusion of superficial femoral artery**

### Percutaneous Nephrostomy
- placement of catheter into renal collecting system
- indications: hydronephrosis, pyonephrosis, ureteric injury with or without urinary peritonitis (traumatic or iatrogenic)
- complications: bacteremia and septic shock, hematuria due to pseudoaneurysm or AV fistulas, injury to adjacent organs

### Gastrostomy/Gastrojejunostomy
- percutaneous placement of catheter directly into either stomach (gastrostomy) or through stomach into small bowel (transgastric jejunostomy)
- indications: inability to eat (most commonly CNS dysfunction, e.g. stroke), esophageal obstruction, or decompression in gastric outlet obstruction
- complications: gastroesophageal reflux with aspiration, peritonitis, hemorrhage, bowel or solid organ injury

### Radiofrequency Ablation
- U/S- or CT-guided probe is inserted into tumour, radiofrequency energy delivered through probe causes heat deposition and tissue destruction
- indications: hepatic tumours (HCC and metastases), renal tumours
- complications: destruction of neighbouring tissues and structures, bleeding, periprocedural embolism

# Breast Imaging

## Modalities

### Mammography

#### Description

- x-ray imaging of the breasts for screening in asymptomatic patients, or diagnosis of clinically-detected or screening-detected abnormalities (see General Surgery, GS61)
- routine evaluation involves two standard views: cranio-caudal and medial-lateral-oblique

#### Indications

- screening
  - begin screening from age 50 q2-3yr
  - no strong data to support screening >70 yr, but may continue screening if in good general health
  - if <50, screening is only recommended for those with high risk of breast cancer
  - screening detects 2-8 cancers/1000 women screened
- surveillance
  - follow-up of women with previous breast cancer
- diagnostic: includes mammography with special views and/or ultrasound
  - workup of an abnormality that may be suggestive of breast cancer including a lump or thickening, localized nodularity, dimpling or contour deformity, a persistent focal area of pain, overlying skin changes, and spontaneous serous or sanguinous nipple discharge from a single duct
  - women with abnormal screening mammograms
  - suspected complications of breast implants

**Table 20. Breast Imaging Reporting and Data System (BI-RADS®) Mammography Categories**

| Assessment Categories | Imaging Findings | Follow-Up Recommendations |
|---|---|---|
| **BI-RADS 0** | Incomplete | Additional imaging<br>Comparison to prior films |
| **BI-RADS 1** | Negative | Routine screening |
| **BI-RADS 2** | Benign | Routine screening |
| **BI-RADS 3** | Probably benign<br>Likelihood of malignancy is <2% | Unilateral mammogram at 6 mo |
| **BI-RADS 4** | Suspicious abnormality | Biopsy |
| **BI-RADS 5** | Highly suspicious of malignancy<br>Likelihood of malignancy is 95% | Biopsy |
| **BI-RADS 6** | Malignancy confirmed by biopsy | Definitive therapy |

### Breast Ultrasound

#### Indications

- characterization of palpable abnormalities
  - ultrasound is 1st line in <30 yr – denser breast tissue makes mammograms less sensitive in young females
  - 1st line in lactating and pregnant women
  - >30 yr need mammogram first
- further characterization of mammographic findings
- guidance for interventional procedures

### Breast MRI

#### Description

- contrast-enhanced MRI of the breasts
- sensitive for detecting invasive breast cancer (95-100%) but specificity variable (37-97%)
- for diagnosis, used only after mammography and U/S investigation
- use as a screening modality is limited to high-risk patients, in conjunction with mammography

#### Indications

- "problem-solving" of indeterminate findings following complete mammographic and ultrasound workup
- evaluation of occult primary in patients presenting with axillary metastases
- evaluation of patients with suspected silicone implant rupture and problems associated with breast implants
- evaluation of previously diagnosed breast cancer: positive margins, recurrence, response to chemotherapy

- high-risk screening
  - known BRCA1 or BRCA2 mutation, or other gene predisposing to breast cancer, or untested first-degree relative of a carrier of such a gene mutation
  - family history consistent with a hereditary breast cancer syndrome and/or estimated personal lifetime cancer risk >25%
  - high-risk marker on prior biopsy (atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma *in situ*)
  - radiation therapy to chest (before age 30)

# Breast Interventional Procedures

### Description
- includes fine needle aspirate biopsy, core needle biopsy, stereotactic biopsy, MRI guided biopsy, abscess drainage, and cyst aspiration

### Indications
- cystic mass: complex cyst, symptomatic, suspected abscess
- solid mass: confirm diagnosis of a lesion suspicious for malignancy (BI-RADS® Category 4 or 5)
- suspicious calcifications: confirm diagnosis of a lesion suspicious for malignancy (BI-RADS® Category 4 or 5) – stereotactic biopsy
- initial percutaneous biopsy procedure that was insufficient or discordant with imaging
- presurgical wire localization of a lesion

# Breast Findings

### Breast Masses
- **definition**: a space-occupying lesion seen in two different projections; if seen in only a single projection it should be called an "asymmetry" until its three-dimensionality is confirmed

**Table 21. Mammographic Features of Benign and Malignant Breast Masses**

| | Benign | Malignant |
|---|---|---|
| **Shape** | Oval, round, lobular | Irregular |
| **Margin** | Circumscribed, well-defined | Indistinct, microlobulated, spiculated |
| **Density** | Radiolucent (oil cyst, lipoma, fibrolipoma, galactocele, hamartoma) | Radiodense |
| **Calcifications (± mass)** | Popcorn (hyalinizing fibroadenoma), lucent centred (oil cyst/fat necrosis), layering (milk of calcium), vascular, round, scattered | Pleomorphic (vary in size and shape), amorphous (indistinct), fine linear, coarse heterogeneous, regional, segmental, clustered |

### Other Findings
- tubular density/dilated duct: branching tubular structures usually represent enlarged ducts (milk ducts); if they are clearly identified as such, these densities are of little concern
- intramammary lymph node: typical lymph nodes are circumscribed, reniform and often have a fatty notch and centre; usually less than 1 cm, and usually seen in the outer, often upper part of the breast; when these characteristics (particularly fatty centre or notch) are well seen, the lesion is almost always benign and insignificant
- focal asymmetry: area of breast density with similar shape on two views, but completely lacking borders and conspicuity of a true mass; must be carefully evaluated with focal compression to exclude findings of a true mass or architectural distortion
- if focal compression shows mass-like character – or if the area can be palpated – biopsy generally recommended

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# NP Nephrology

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# Acronyms

| | |
|---|---|
| ACEI | angiotensin converting enzyme inhibitor |
| ACR | albumin to creatinine ratio |
| ADH | antidiuretic hormone |
| AG | anion gap |
| AIN | acute interstitial nephritis |
| AKI | acute kidney injury |
| ANA | antinuclear antibody |
| ARB | angiotensin receptor blocker |
| ASA | acetylsalicylic acid |
| ASOT | anti-streptolysin-O titer |
| ATN | acute tubular necrosis |
| AVM | arteriovenous malformation |
| c-ANCA | cytoplasmic antineutrophil cytoplasmic antibody |
| C&S | culture and sensitivity |
| CHF | congestive heart failure |
| CKD | chronic kidney disease |
| Cr | creatinine |
| CrCl | creatinine clearance |
| D5W | 5% dextrose in water |
| DCT | distal convoluted tubule |
| DDAVP | 1-desamino-8-d-arginine vasopressin |
| DI | diabetes insipidus |
| DIC | disseminated intravascular coagulation |
| DKA | diabetic ketoacidosis |
| DM | diabetes mellitus |
| ECF | extracellular fluid |
| eGFR | estimated glomerular filtration rate |
| ESR | erythrocyte sedimentation rate |
| ESRD | end-stage renal disease |
| $FE_{Na^+}$ | fractional excretion of sodium |
| FF | filtration fraction |
| FSGS | focal segmental glomerulosclerosis |
| GBM | glomerular basement membrane |
| GFR | glomerular filtration rate |
| GN | glomerulonephritis |
| HCTZ | hydrochlorothiazide |
| HPF | high power field |
| HSP | Henoch-Schönlein purpura |
| HTN | hypertension |
| HUS | hemolytic uremic syndrome |
| IVP | intravenous pyelogram |
| LOC | level of consciousness |
| MDRD | modification of diet in renal disease |
| NS | normal saline |
| p-ANCA | perinuclear anti-neutrophil cytoplasmic antibody |
| PKD | polycystic kidney disease |
| PTH | parathyroid hormone |
| R&M | routine and microscopy |
| RAAS | renin-angiotensin-aldosterone system |
| RBF | renal blood flow |
| RCC | renal cell carcinoma |
| RPF | renal plasma flow |
| RPGN | rapidly progressive glomerulonephritis |
| RRT | renal replacement therapy |
| RTA | renal tubular acidosis |
| SIADH | syndrome of inappropriate antidiuretic hormone |
| SLE | systemic lupus erythematosis |
| TBW | total body water |
| TIN | tubulointerstitial nephritis |
| TTP | thrombotic thrombocytopenic purpura |
| UAG | urine anion gap |
| UTI | urinary tract infection |

# Basic Anatomy Review

## Embryology of the Kidney

- intermediate mesodermic origin
- pronephros (from nephrogenic cord growing caudally towards cloaca) develops at the end of week 3 and then degenerates along with adjacent pronephric duct
- mesonephros develops in 4th week, degenerates, and the remnants form the mesonephric (Wolffian) duct of the male reproductive system
- metanephros develops in the 5th week from the ureteric bud in the mesonephric duct into the metanephric (mesoderm-derived) mass
  - ureteric bud → ureters, renal pelvis, calyces, collecting ducts
  - metanephric mass → nephrons (from glomeruli to the DCT)
  - kidneys ascend from the pelvis into the retroperitoneum rotating medially while ascending, and gaining a blood supply from the renal arteries as they ascend

## Renal Structure and Function

### The Nephron

- basic structural and functional unit of the kidney, approximately 1 million per kidney
- 2 main components: glomerulus and attached renal tubule
- direction of blood flow: afferent arteriole → glomerular capillaries → efferent arteriole → vasa recta (the capillaries surrounding the tubules) → renal venules

**Table 1. Major Kidney Functions**

| Function | Mechanism | Affected Elements |
|---|---|---|
| **1. Waste Excretion** | Glomerular filtration | Excretion of nitrogenous products of protein metabolism (urea, Cr) |
| | Tubular secretion | Excretion of organic acids (urate) and organic bases (Cr) |
| | Tubular catabolism | Breakdown and excretion of drugs (antibiotics, diuretics) and peptide hormones (most pituitary hormones, insulin, glucagon) |
| **2. Electrolyte Balance and Osmoregulation** | Tubular NaCl and water reabsorption | Controls volume status and osmolar balance |
| | Tubular $K^+$ secretion | Controls potassium concentration |
| | Tubular $H^+$ secretion | Acid-base balance |
| | $HCO_3^-$ synthesis and reabsorption | Acid-base balance |
| | Tubular $Ca^{2+}$, $Mg^{2+}$, $PO_4^{3-}$ transport | Alters $Ca^{2+}$, $Mg^{2+}$, $PO_4^{3-}$ homeostasis |
| | Synthesize osmolytes | Increase osmolality of medullary cytoplasm to match medullary concentration gradient |
| **3. Hormonal Synthesis** | Erythropoietin production (cortex) | Red blood cell production |
| | Vitamin D activation: 25(OH)VitD converted to 1,25$(OH)_2$VitD (proximal tubule) | Calcium homeostasis |
| | Renin production (juxtaglomerular apparatus) | Alters vascular resistance and aldosterone secretion |
| **4. Blood Pressure Regulation** | $Na^+$ excretion | Alters ECF volume |
| | Renin production | Alters vascular resistance |
| **5. Glucose Homeostasis** | Gluconeogenesis (from lactate, pyruvate, and amino acids) | Glucose supply maintained in prolonged starvation |
| | Clearance and degradation of circulating insulin | Maintains glucose homeostasis |

## The Glomerulus

- site where blood constituents are filtered through to the kidney tubules for excretion or reabsorption
- filtration occurs across the glomerular filtration barrier (endothelium, GBM, podocytes) into Bowman's space
- there is a filtration barrier to albumin due to its size and negative charge. The negative charge of the GBM repels the negatively charged albumin
- consists of following cell types:
  1. Mesangial cells
     - structural cells that support the glomerular capillaries; also has contractile activity and can alter GFR
     - also secretory cells under physiological and pathophysiological conditions, secreting matrix components, pro- and anti-inflammatory cytokines and chemokines
  2. Capillary endothelial cells
     - one of the cells of the glomerular filtration barrier; help form the plasma filtration apparatus due to their sinusoidal nature and glycocalyx; contribute to the production of the GBM
     - interface with blood – target for antibodies and contact site for neutrophils, lymphocytes
3. Visceral epithelium (podocytes)
   - one of the cells of the glomerular filtration barrier; helps form the plasma filtration apparatus due to their interdigitated foot process forming slit diaphragms; contribute to the production of extracellular matrix proteins (collagen and laminin) making up the GBM
  4. Parietal epithelium
     - lines the interior of Bowman's capsule and contains a podocyte progenitor population
  5. Juxtaglomerular cells
     - smooth muscle cells in lining of afferent arteriole; produce, store and secrete renin

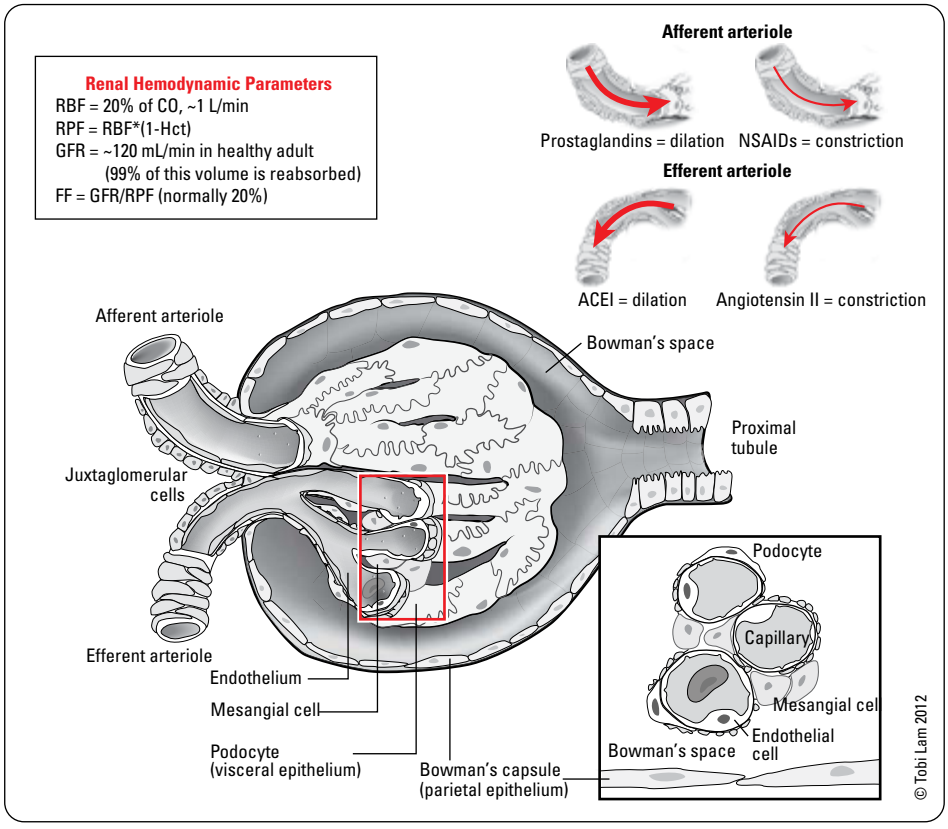



**Figure 1. The glomerulus**

## The Renal Tubules

- reabsorption and secretion occur between the renal tubules and vasa recta forming urine for excretion
- each segment of the tubule selectively transports various solutes and water and is targeted by specific diuretics

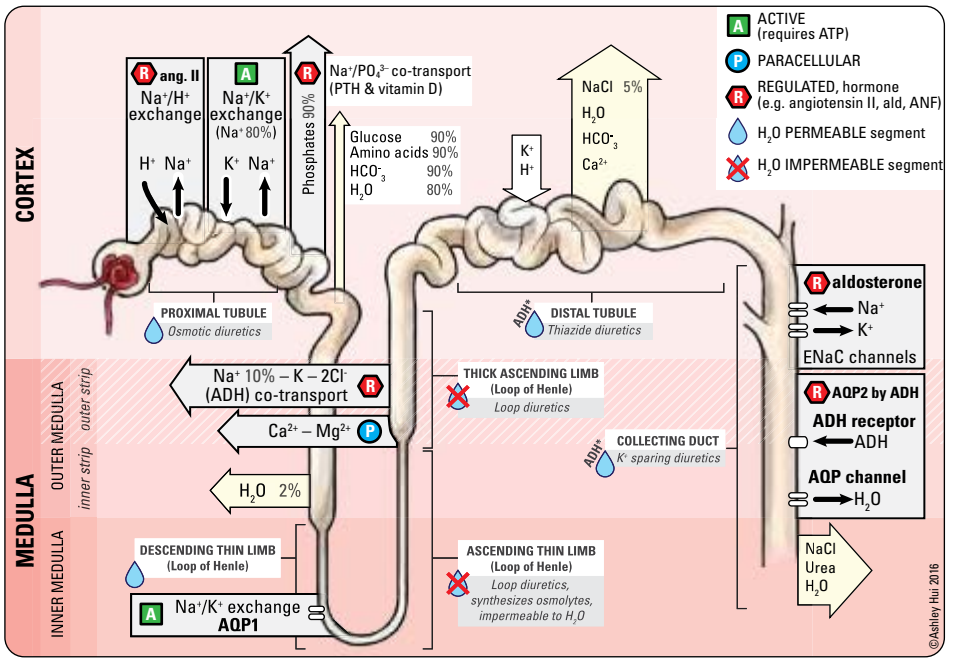



**Figure 2. Tubular segments of the nephron**

# Renal Hemodynamics

- GFR
  - GFR is the sum of the filtration across all nephrons
  - the rate of fluid transfer between glomerular capillaries and Bowman's space
  - average GFR of 180 L/d or 125mL/min/1.73m$^2$, of which 99% of the filtrate is reabsorbed
  - normal urine output is 0.5-2.0 mL/kg/h in adults
  - GFR is highest in early adulthood, and decreases thereafter starting around age 40
- renal autoregulation maintains constant GFR over mean arterial pressures of 70-180 mmHg
- 2 mechanisms of autoregulation to maintain GFR homeostasis
  - myogenic mechanism: release of vasoactive factors in response to changes in perfusion pressure (e.g. low GFR → decreased perfusion pressure → release of prostaglandin → afferent arteriolar dilation → increased GFR)
  - tubuloglomerular feedback: changes in $Na^+$ delivery to macula densa lead to changes in afferent arteriolar tone (e.g. high GFR → increased $Na^+$ delivery → afferent constriction → decreased GFR)
- Filtration fraction
  - percentage of RPF filtered across the glomeruli
  - expressed as a ratio: FF = GFR/RPF; normal = 0.2 or 20%
  - angiotensin II constricts renal efferent arterioles which increases FF, thereby maintaining GFR
- renin is released from juxtaglomerular apparatus in response to decreased RPF and maintains sodium balance
  - renin is an important enzyme in the renin angiotensin aldosterone system, that converts angiotensinogen to angiotensin I

**Glomerular Filtration Rate**
GFR = Kf ($\Delta P - \Delta \Pi$)
Kf = ultrafiltration coefficient
$\Delta P$ = hydrostatic pressure difference between glomerular capillaries and Bowman's space
$\Delta \Pi$ = osmotic pressure difference between glomerular capillaries and Bowman's space
$\Delta P - \Delta \Pi$ = net outward pressure

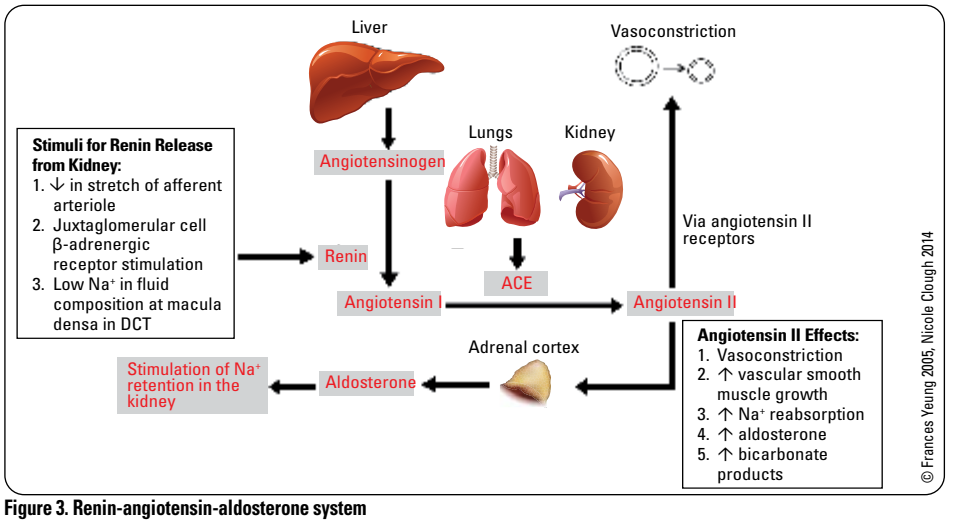



**Figure 3. Renin-angiotensin-aldosterone system**

# Assessment of Renal Function

## Measurement of Renal Function

- clinically, GFR is estimated using serum creatinine concentration, [Cr]
- inulin clearance and iothalamate radiotracer are the gold standard for measuring GFR, but very rarely used clinically
- most renal functions decline in parallel with a decrease in GFR
- Cr is a metabolite of creatine phosphate (intermediate in muscle metabolism), therefore increased muscle mass increases Cr production (thus the need to use body mass, ethnic origin, age, and gender in order to estimate GFR)
- Cr is freely filtered at the glomerulus with little tubular reabsorption
- tubular secretion of Cr varies based on level of renal function (10% to >50%)
- Cr filtered ≈ Cr excreted (at steady state)

### Ways to Estimate GFR Using Serum Creatinine Concentration

1. Estimate GFR using CKD-EPI equation
   - the best current equation
   - calculated using serum Cr, age, sex, and race
   - overestimate GFR
2. Estimate GFR using MDRD formula
   - most common way in which GFR is estimated (MDRD 7 equation)
   - complex formula incorporating age, gender, serum Cr, and race, but does not include weight
   - GFR is reported as mL/min/1.73 $m^2$ body surface area
   - underestimation of GFR at near normal values
3. Measure CrCl – 24 h urine collection
   - calculation provides reasonable estimate of GFR
   - GFR/d = (urine [Cr] x 24 h urine volume)/(plasma [Cr])
   - must use same units for urine [Cr] and plasma [Cr]
4. Estimate CrCl using Cockcroft-Gault formula
   - serum Cr used along with age, gender, and weight (kg) to estimate GFR (but does not include race)
   - overestimates GFR when renal function severely impaired
   - does not account for variations in body tissue composition

### Limitations of Using Serum Cr Measurements

1. must be in steady state
   - constant GFR and rate of production of Cr from muscles
   - sudden injury (e.g. AKI) may reduce GFR substantially, however, serum Cr will not immediately reflect sudden reduction in GFR until new Cr steady-state is reached
2. GFR must fall substantially before plasma [Cr] rises above normal laboratory range
   - with progressive renal failure, remaining nephrons compensate with hyperfiltration
   - GFR is relatively preserved despite significant structural damage
3. plasma [Cr] is influenced by the rate of Cr production
   - lower production with smaller muscle mass (e.g. female, elderly, low weight)
     - for example, consider plasma [Cr] of 100 µmol/L in both of these patients
       - 20 yr old lean man who weighs 100 kg, GFR = 144 mL/min
       - 80 yr old woman who weighs 50 kg, GFR = 30.6 mL/min
   - clinical correlation: GFR decreases with age but would not be reflected as a rise in serum Cr due to the age-associated decline in muscle mass
4. tubular secretion of Cr increases as GFR decreases
   - serum Cr and CrCl overestimate low GFR
   - certain drugs (cimetidine, trimethoprim) interfere with Cr secretion
5. errors in Cr measurement
   - very high bilirubin level causes [Cr] to be falsely low
   - acetoacetate (a ketone body) and certain drugs (cefoxitin) create falsely high [Cr]

### Measurement of Urea Concentration

- urea is the major end-product of protein metabolism
- plasma urea concentration reflects renal function but should not be used alone as it is modified by a variety of other factors
- urea production reflects dietary intake of protein and catabolic rate; increased protein intake or catabolism (sepsis, trauma, GI bleed) causes increase in urea level
- ECF volume depletion causes a rise in urea independent of GFR or plasma [Cr]
- in addition to filtration, a significant amount of urea is reabsorbed along the tubule
- reabsorption is increased in hypernatremic states
- typical ratio of urea to [Cr] in serum is 1:12 in SI units (using mmol/L for urea and µmol/L for Cr)



$Cr_{filtered} = Cr_{excreted}$

$[Cr]_{plasma} \times GFR = [Cr]_{urine} \times$ urine flow rate (mL/min)

$GFR = \frac{[Cr]_{urine} \times \text{urine flow rate}}{[Cr]_{plasma}}$



At steady state $[Cr]_{serum} \propto 1/CrCl$



**Cockcroft-Gault Formula**

$CrCl\ (mL/min) = \frac{(\text{weight in kg})\ (140-\text{age}) \times 1.23}{(\text{serum creatinine } (\mu mol/L)}$

Multiply above by 0.85 for females



**MDRD Equation**

$GFR\ (mL/min/1.73\ m^2) = 186 \times (CrS)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ for females}) \times (1.212 \text{ if black})$



**CKD-EPI Equation**

$GFR\ (mL/min/1.73\ m^2) = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{age} \times (1.018 \text{ if female}) \times (1.159 \text{ if black})$

$\kappa = 0.7$ for females and 0.9 for males

$\alpha = -0.329$ for females and -0.411 for males

min indicates the minimum of $SCr/\kappa$ or 1

max indicates the maximum of $SCr/\kappa$ or 1



**Cystatin C**

Cystatin C is a protease which is completely filtered by the glomerulus and is not affected by muscle mass; it is not currently used in clinical practice, but may be a more accurate way to measure renal function in the future, particularly in DM



**Clinical Settings in which Urea Level is Affected Independent of Renal Function**

**Disproportionately High Urea**

- Volume depletion (prerenal azotemia)
- GI hemorrhage
- High protein diet
- Sepsis
- Catabolic state with tissue breakdown
- Corticosteroid or cytotoxic agents

**Disproportionately Low Urea**

- Low protein diet
- Liver disease

# Urinalysis

- use dipstick in freshly voided urine specimen to assess the following:

### 1. Specific Gravity
- ratio of the mass of equal volumes of urine/$H_2O$
- range is 1.001-1.030
- values <1.010 reflect dilute urine, values >1.020 reflect concentrated urine
- value usually 1.010 (isosthenuria: same specific gravity as plasma) in ESRD

**Estimating Urine Osmolality**
Last 2 digits of the specific gravity x 30 = urine osmolality approximately
(e.g. specific gravity of 1.020 = 600 mOsm)

### 2. pH
- urine pH is normally between 4.5-7.0; if persistently alkaline, consider
  - RTA
  - UTI with urease-producing bacteria (e.g. *Proteus*)

**24 h Urine Collection**
- Discard first morning specimen
- Collect all subsequent urine for the next 24 h
- Refrigerate between voids
- Collect second morning specimen and take to lab immediately

### 3. Glucose
- freely filtered at glomerulus and reabsorbed in proximal tubule
- causes of glycosuria include:
  1. hyperglycemia >9-11.1 mmol/L leads to filtration that exceeds tubular resorption capacity
  2. increased GFR (e.g. pregnancy - the proximal convoluted tubule is unable to reabsorb the glucose and amino acids)
  3. proximal tubule dysfunction (e.g. Fanconi's syndrome)
  4. sodium-glucose cotransporter 2 (SGLT2) inhibitors (also known as -flozin drugs) which are prescribed for DM2; lower the threshold for glucosuria by preventing glucose reabsorption from the filtrate

### 4. Protein
- dipstick only detects albumin; other proteins (e.g. Bence-Jones, Ig, Tamm-Horsfall) may be missed
- microalbuminuria (morning ACR of 2.0 - 20 mg/mmol) is not detected by standard dipstick; greater than these ranges would be macroalbuminuria
- gold standard: 24 h timed urine collection for total protein

Positive dipstick for leukocyte esterase and nitrites is highly specific for diagnosing a UTI

### 5. Leukocyte Esterase
- enzyme found in WBC and detected by dipstick
- presence of WBCs indicates infection (e.g. UTI) or inflammation along the urinary tract including prostate, bladder, ureter, pelvis and interstitium (e.g. AIN)

**Nitrite Negative Bacteria**
- *Enterococci*
- *Staphylococci*

### 6. Nitrites
- endogenous nitrates in urine are converted to nitrites by some bacteria (most commonly *E. coli*)
- high specificity but low sensitivity for UTI

**Nitrite Positive Bacteria**
- *Enterobacteriacae* (e.g. *E. coli*)

### 7. Ketones
- positive in alcoholic/diabetic ketoacidosis, prolonged starvation, fasting

### 8. Hemoglobin
- positive in hemoglobinuria (hemolysis), myoglobinuria (rhabdomyolysis), and true hematuria (RBCs seen on microscopy)

# Urine Microscopy

**Table 2. Comparison of Urinary Sediment Findings**

| | Active Sediment = Suggestive of Parenchymal Kidney Disease | Bland Sediment = Less Likely Parenchymal Kidney Disease |
|---|---|---|
| **Any one or more of the following seen on microscopy** | Red cell casts | Only hyaline casts |
| | White cell casts | Small quantities of crystals |
| | Muddy-brown granular or epithelial cell casts | Small amount of bacteria |
| | >2 red cells per HPF | <2 red cells per HPF |
| | >4 white cells per HPF | <4 white cells per HPF |

### 1. CELLS

### Erythrocytes
- hematuria = >2 RBCs per HPF
- dysmorphic RBCs and/or RBC casts suggest glomerular bleeding (e.g. proliferative GN)
- isomorphic RBCs, no casts suggest extraglomerular bleeding (e.g. bladder cancer)

### Leukocytes
- pyuria = greater than upper limit of normal: >4 WBCs per HPF
- indicates inflammation or infection
- if persistent sterile pyuria present (i.e. negative culture), consider: chronic urethritis, prostatitis, interstitial nephritis, calculi, allergic cystitis, interstitial cystitis, papillary necrosis, renal tuberculosis, viral infections, *N. gonorrhoeae, C. trachomatis* infection

### Eosinophils
- detected using Wright's or Hansel's stain (not affected by urine pH)
- consider AIN, atheroembolic disease

### Oval Fat Bodies
- renal tubular cells filled with lipid droplets
- seen in heavy proteinuria (e.g. nephrotic syndrome)

### 2. CASTS
- cylindrical structures formed by intratubular precipitation of Tamm-Horsfall mucoprotein; cells may be trapped within the matrix of protein

**Table 3. Interpretation of Casts**

| Casts | Interpretation |
|---|---|
| **Hyaline casts** | Physiologic (concentrated urine, fever, exercise) |
| **RBC casts** | Glomerular bleeding (Proliferative GN, vasculitis) |
| **WBC casts** | Infection (pyelonephritis)<br>Inflammation (interstitial nephritis) |
| **Pigmented granular casts (heme granular casts, muddy brown)** | ATN<br>Acute proliferative GN |
| **Fatty casts** | Nephrotic syndrome (>3.5 g/d) |

### 3. CRYSTALS
- uric acid: consider acidic urine, hyperuricosuria, tumour lysis syndrome
- calcium phosphate: alkaline urine
- calcium oxalate: consider hyperoxaluria, ethylene glycol poisoning, nephrolithiasis
- sulfur: sulfa-containing antibiotics

## Urine Biochemistry

- commonly measure: $Na^+$, $K^+$, $Cl^-$, osmolality, and pH
- spot urine more useful to assess renal physiology, 24 h urine collection more reflective of mineral balance
- no "normal" values; electrolyte excretion depends on intake and current physiological state
- results must be interpreted in the context of a patient's current state, for example:

1. ECF volume depletion: expect low urine $[Na^+]$ (kidneys should be retaining $Na^+$)
   - urine $[Na^+]$ >20 mmol/L suggests a renal problem or the action of a diuretic
   - urine $[Na^+]$ <20 mmol/L suggests a prerenal problem
2. daily urinary potassium excretion rate should be decreased (<20 mmol/d) in hypokalemia
   - if higher than 20 mmol/d, suggests renal contribution to hypokalemia

- osmolality is useful to estimate the kidney's concentrating ability
- $FE_{Na}$ refers to the fractional excretion of $Na^+$ (Na excreted in urine/Na filtered through kidney)
  - $FE_{Na}$ <1% suggests the pathology is prerenal
- urine pH is useful to grossly assess renal acidification
  - low pH (<5.5) in the presence of low serum pH is an appropriate renal response
  - a high pH in this setting might indicate a renal acidification defect (e.g. RTA Type 1)



**Fractional Excretion of Sodium**

$$FE_{Na} = \frac{[Na^+]_{urine} \times [Cr]_{plasma}}{[Na^+]_{plasma} \times [Cr]_{urine}} \times 100$$

# Electrolyte Disorders

## Sodium Homeostasis

- hyponatremia and hypernatremia are disorders of water balance
  - hyponatremia usually suggests too much water in the ECF relative to $Na^+$ content
  - hypernatremia usually suggests too little water in the ECF relative to $Na^+$ content
- solutes (such as $Na^+$, $K^+$, glucose) that cannot freely traverse the plasma membrane contribute to effective osmolality and induce transcellular shifts of water
  - water moves out of cells in response to increased ECF osmolality
  - water moves into cells in response to decreased ECF osmolality
- ECF volume is determined by $Na^+$ content rather than concentration
  - $Na^+$ deficiency leads to ECF volume contraction
  - $Na^+$ excess leads to ECF volume expansion
- clinical signs and symptoms of hyponatremia and hypernatremia are secondary to cells (especially brain cells) shrinking (hypernatremia) or swelling (hyponatremia)

**Table 4. Clinical Assessment of ECF Volume* (Total Body $Na^+$)**

| Fluid Compartment | Hypovolemic | Hypervolemic |
|---|---|---|
| **Intravascular** | | |
| JVP | Decreased | Increased |
| Blood pressure | Orthostatic drop | Normal to increased |
| Auscultation of heart | Tachycardia | S3 |
| Auscultation of lungs | Normal | Inspiratory crackles |
| **Interstitial** | | |
| Skin turgor | Decreased | Normal/increased |
| Edema (dependent) | Absent | Present |
| **Other** | | |
| Urine output | Decreased** | Variable |
| Body weight | Decreased | Increased |
| Hematocrit, serum protein | Increased | Decreased |
| Urine sodium | Increased | Decreased |

*Refers to effective circulating volume (ECV), which is the ECF volume adequately perfusing tissues.
**If there is a renal abnormality (e.g. osmotic diuresis), the urine output may be increased despite the presence of hypovolemia

# Hyponatremia

- hyponatremia: serum [$Na^+$] <135 mmol/L
- can be associated with hypo-osmolality (most common), iso-osmolality, or hyperosmolality
- consider if it is associated with "appropriate" (hypovolemia) vs. "inappropriate" (euvolemia) ADH secretion
- if appropriate ADH secretion, is it real vs. effective volume loss?

If the urine osmolality is unknown, assume the urine is hypo-osmolar/dilute

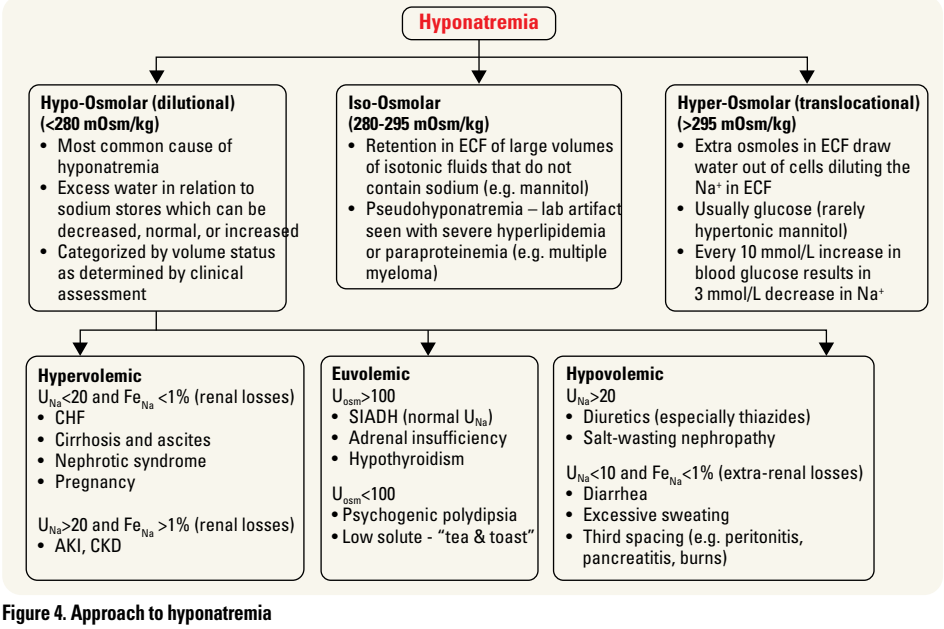



**Figure 4. Approach to hyponatremia**

## Signs and Symptoms

- depend on degree of hyponatremia and more importantly, velocity of progression from onset
- hyponatremia = swollen cells
- acute hyponatremia (<24-48 h) more likely to be symptomatic
- chronic hyponatremia (>24-48 h) less likely to be symptomatic due to adaptation
  - adaptation: normalization of brain volume through loss of cellular electrolytes (within hours) and organic osmolytes (within days)
- neurologic symptoms predominate (secondary to cerebral edema): headache, nausea, malaise, lethargy, weakness, muscle cramps, anorexia, somnolence, disorientation, personality changes, depressed reflexes, decreased LOC

## Complications

- seizures, coma, respiratory arrest, permanent brain damage, brainstem herniation, death
- risk of brain cell shrinkage with rapid correction of hyponatremia
  - can develop osmotic demyelination of pontine and extrapontine neurons; may be irreversible (e.g. central pontine myelinolysis)
  - symptom onset may be delayed 2-6 d; begins as dysarthria, dysphagia, paresis, movement disorders → later on seizures, lethargy, confusion, disorientation, obtundation, coma

**Symptoms of Central Pontine Myelinolysis**
- Cranial nerve palsies
- Quadriplegia
- Decreased LOC

### Risk Factors for Osmotic Demyelination
- rise in serum [$Na^+$] with correction >8 mmol/L/24 h if chronic hyponatremia
- associated hypokalemia and/or malnutrition (e.g. low muscle mass)
- if patient with hyponatremia and hypovolemia is given large volume of isotonic fluid (ADH is stimulated by hypovolemia; when hypovolemia is corrected, the ADH level falls suddenly causing sudden brisk water diuresis, and therefore rapid rise in serum $Na^+$ level)
- patient with psychogenic polydipsia who is subsequently deprived of water

### Investigations
- ECF volume status assessment (see Table 4)
- serum electrolytes, glucose, Cr
- serum osmolality, urine osmolality
- urine Na+ (urine $Na^+$ <10-20 mmol/L suggests volume depletion as the cause of hyponatremia)
- assess for causes of SIADH (see Table 5)
- TSH, free T4, and cortisol levels
- consider CXR and possibly CT chest if suspect pulmonary cause of SIADH (e.g. paraneoplastic syndrome by small cell lung cancer)
- consider CT head if suspect CNS cause of SIADH (i.e. subarachnoid hemorrhage)

### Treatment of Hyponatremia
- general measures for all patients
  1. treat underlying cause (e.g. restore ECF volume if volume depleted, remove offending drug, treat pain, nausea, etc.)
  2. restrict free water intake in SIADH (<1000 mL/d)
  3. promote free water loss
  4. carefully monitor serum Na+, urine volume, and urine tonicity
  5. monitor frequently that correction is not too rapid
- monitor urine output frequently: high output of dilute urine is the first sign of dangerously rapid correction of hyponatremia as the stimulus for ADH is diminished with the correction of hypovolemia

**A. Known Acute (known to have developed over <24-48 h)**
- commonly occurs in hospital (dilute IV fluid, post-operative increased ADH)
- less risk from rapid correction since adaptation has not fully occurred
- if symptomatic
  - correct rapidly with 3% NaCl 1-2 cc/kg/h up to serum [$Na^+$] = 125-130 mmol/L
  - may need furosemide to address volume overload
- if asymptomatic, treatment depends on level of serum sodium
  - if serum [$Na^+$] >120 mmol/L, take general measures to identify and reverse cause of hyponatremia
  - if serum [$Na^+$] <120 mmol/L, treat as symptomatic
  - can consider giving 3% NaCl to prevent further deterioration in serum sodium
  - do not give 3% NaCl if hyponatremia is autocorrecting due to water diuresis

**B. Chronic or Unknown**
1. if severe symptoms (seizures or decreased LOC)
   - must partially correct acutely
   - aim for increase of $Na^+$ by 0.5-1 mmol/L/h for 4-6 h
   - limit total rise to 8 mmol/L in 24 h
   - IV 3% NaCl at 1-2 cc/kg/h
   - may need furosemide
2. if asymptomatic
   - water restrict to <1 L/d fluid intake
   - consider IV 0.9% NS + furosemide (reduces urine osmolality, augments excretion of $H_2O$)
   - consider NaCl tablet or Oxocubes® as a source of $Na^+$
3. refractory
   - furosemide and oral salt tablets
   - oral urea (osmotic aquaresis)
   - "vasopressin receptor 2 antagonists (e.g. tolvaptan)
4. always pay attention to patient's ECF volume status – if already volume-expanded, usually don`t give NaCl (tablet or IV); if already volume-depleted, almost never appropriate to give furosemide

**C. Options for Treatment of Overly-Rapid Correction**
- give water (IV D5W)
- give ADH to stop water diuresis (DDAVP 1-2 µg IV)

### Impact of IV Solution on Serum [$Na^+$]
- formula to estimate the change in serum [$Na^+$] caused by retention of 1 L of any infusate

[TBW = (for men) 0.6 x weight(kg); (for women) 0.5 x weight(kg)]

$$\text{change in serum } [Na^+] = \frac{\text{infusate } [Na^+] - \text{serum } [Na^+]}{\text{TBW} + 1\text{ L}}$$

- formula assumes there are no losses of water or electrolytes



**Beware of Rapid Correction of Hyponatremia**
- Inadvertent rapid correction of hyponatremia can easily occur (e.g. patient with hyponatremia due to SIADH from nausea)
  - Anti-emetic given for relief of hyponatremia-induced nausea
  - ADH quickly turned off in the absence of nausea, the kidneys rapidly excrete the excess free water, and the serum [Na+] rises rapidly
- Patient at risk of osmotic demyelination
- High output dilute urine (>100 cc/h, <100 mOsm/L) in the setting of hyponatremia is usually the first sign of dangerously rapid correction of serum sodium



Correction of $Na^+$ in hyponatremia should not exceed 8 mmol/L/24 h unless definitely known to be <24-48 h duration; frequent monitoring of serum $Na^+$ and urine output is essential



**Concentration of [$Na^+$] in Common Infusates**
- [$Na^+$] in 0.45% NaCl = 77 mmol/L
- [$Na^+$] in 0.9% NaCl = 154 mmol/L
- [$Na^+$] in 3% NaCl = 513 mmol/L
- [$Na^+$] in 5% NaCl = 855 mmol/L
- [$Na^+$] in Ringer's lactate = 130 mmol/L
- [$Na^+$] in D5W = 0

## SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION

1. urine that is inappropriately concentrated for the serum osmolality
2. urine sodium >20-40 mmol/L – likely reflecting euvolemia
3. $FE_{Na}$ >1%

**Table 5. Disorders Associated with SIADH**

| Cancer | Pulmonary | CNS | Drugs | Miscellaneous |
|---|---|---|---|---|
| Small cell cancer<br>Bronchogenic carcinoma<br>Pancreatic adenocarcinoma<br>Hodgkin's lymphoma<br>Thymoma<br>Leukemia | Pneumonia<br>Lung abscess<br>Tuberculosis<br>Acute respiratory failure<br>Asthma<br>COPD<br>Positive pressure ventilation | Mass lesion<br>Encephalitis<br>Subarachnoid hemorrhage<br>Stroke<br>Head trauma<br>Acute psychosis<br>Acute intermittent porphyria | Antidepressants<br>TCAs<br>SSRIs<br>Antineoplastics<br>Vincristine<br>Cyclophosphamide<br>Anti-epileptics<br>Carbamazepine<br>Barbiturates<br>Chlorpropamide<br>ACEI<br>Other<br>DDAVP<br>Oxytocin<br>Nicotine | Post-operative state<br>Pain<br>Severe nausea<br>HIV |

# Hypernatremia

- hypernatremia: serum [$Na^+$] >145 mmol/L
- too little water relative to total body Na+; always a hyperosmolar state
- usually due to NET water loss or insufficient intake, rarely due to hypertonic $Na^+$ gain
- less common than hyponatremia because patients are protected against hypernatremia by thirst and release of ADH

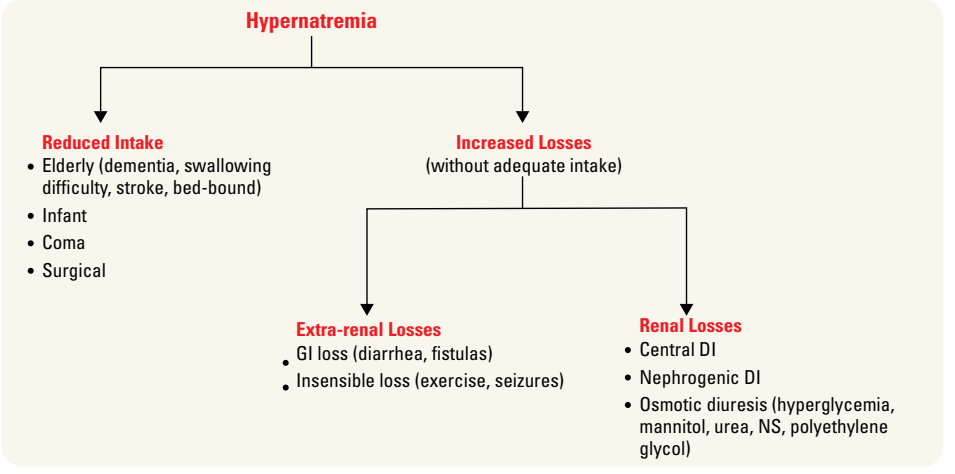



**Figure 5. Approach to hypernatremia**

### Signs and Symptoms

- hypernatremia = shrunken cells
  - acute hypernatremia (<24-48 h)
  - chronic hypernatremia (>24-48 h), cells will have achieved adaptive mechanism: can import and generate new osmotically active particles to normalize cell size
  - nearly all cases of hypernatremia will be due to chronic hypernatremia
  - acute hypernatremia primarily presents in patients with diabetes insipidus
  - symptoms due to brain cell shrinkage: altered mental status, weakness, neuromuscular irritability, focal neurologic deficits, seizures, coma, death
- ± polyuria, thirst, signs of hypovolemia

### Complications

- increased risk of vascular rupture resulting in intracranial hemorrhage
- rapid correction may lead to cerebral edema

### Treatment of Hypernatremia

- general measures for all patients
  - give free water (oral or IV)
  - treat underlying cause
  - monitor serum $Na^+$ frequently (q4h) to ensure correction is not occurring too rapidly

**$H_2O$ Deficit and TBW Equations**
TBW = 0.6 x wt (kg) men
TBW = 0.5 x wt (kg) women

$H_2O$ deficit = TBW x ([$Na^+$]plasma – 140) / 140

Correction of serum [$Na^+$] in hypernatremia should not exceed 12 mmol/L/24 h

1 L D5W approximately equals 1 L of free water
1 L 0.45% NS approximately equals 500 mL of free water

- if evidence of hemodynamic instability, then must first correct volume depletion with NS bolus
- loss of water is often accompanied by loss of $Na^+$, but a proportionately larger water loss
- encourage patient to drink pure water, as oral route is preferred for fluid administration
- if unable to replace PO or NG, correct $H_2O$ deficit with hypotonic IV solution (IV D5W, 0.45% NS [half normal saline], or 3.3% dextrose with 0.3% NaCl ["2/3 and 1/3"])
- chronic hypernatremia – aim to lower serum sodium by 8-10 mEq/L in 24 h (often achieved by giving free water at 1.35 mL/kg/h)
- acute hypernatremia – use formula to calculate water deficit. Replace entire water deficit within 24 h (hourly infusion rate = water deficit in mL/24 h)
- infusion rate may need to be increased in order to account for ongoing losses in addition to initial deficit

# Diabetes Insipidus

- collecting tubule is impermeable to water due to absence of ADH or impaired response to ADH
- defect in central release of ADH (central DI) or renal response to ADH (nephrogenic DI)

### Etiology
- central DI: neurosurgery, granulomatous diseases, trauma, vascular events, and malignancy
- nephrogenic DI
  - usually acquired – drugs (e.g. lithium), secondary to amyloidosis, sickle cell disease, Sjogren syndrome, polycystic kidney disease, electrolyte imbalances (i.e. hypercalcemia)
  - congenital/hereditary

### Diagnosis
- urine osmolality inappropriately low in patient with hypernatremia (Uosm <300 mOsm/kg)
- serum vasopressin concentration may be absent /low (central), or elevated (nephrogenic)
- dehydration test: $H_2O$ deprivation until loss of 3% of body weight or until urine osmolality rises above plasma osmolality; if urine osmolality remains <300 (fails to concentrate urine), most likely DI
- central DI: administer DDAVP (exogenous ADH) (10 μg intranasally or 2 μg SC or IV)
  - nephrogenic DI: exogenous ADH fails to concentrate urine as kidneys do not respond
- treat with water (IV D5W or PO water), thiazides may help as well (thiazides induce hypovolemia → stimulate proximal tubular reabsorption of sodium and water → less delivery of glomerular filtrate to the collecting duct → lower urine volume results)

# Potassium Homeostasis

- approximately 98% of total body $K^+$ stores are intracellular
- normal serum $K^+$ ranges from 3.5-5.0 mEq/L
- in response to $K^+$ rise, rapid removal from ECF is necessary to prevent life-threatening hyperkalemia (K= >6.5 mEq/L)
- insulin, catecholamines, and acid-base status influence $K^+$ movement into cells
  - aldosterone has a minor effect
- potassium excretion is regulated at the distal tubule
  - $K^+$ excretion = urine flow rate x urine $[K^+]$

### Factors which Increase Renal $K^+$ Loss
- hyperkalemia
- increased distal tubular urine flow rate and $Na^+$ delivery (thiazides and loop diuretics)
- increased aldosterone activates epithelial sodium channels in cortical collecting duct, causing $Na^+$ reabsorption and $K^+$ excretion
- metabolic alkalosis (increases $K^+$ secretion)
- hypomagnesemia
- increased non-reabsorbable anions in tubule lumen: $HCO_3^-$, penicillin, salicylate (increased tubular flow rate increases $K^+$ secretion)

# Hypokalemia



- serum $[K^+]$ <3.5 mEq/L

### Signs and Symptoms
- usually asymptomatic, particularly when mild (3.0-3.5 mmol/L)
- nausea/vomiting, fatigue, generalized weakness, myalgia, muscle cramps, and constipation
- if severe: arrhythmias, muscle necrosis, and rarely paralysis with eventual respiratory impairment
- arrhythmias occur at variable levels of $K^+$; more likely if digoxin use, hypomagnesemia, or CAD
- ECG changes are more predictive of clinical picture than serum $[K^+]$
  - U waves most important (low amplitude wave following a T wave)
  - flattened or inverted T waves
  - depressed ST segment
  - prolongation of Q-T interval
  - sinus bradycardia
  - with severe hypokalemia: P-R prolongation, wide QRS, arrhythmias; increases risk of digitalis toxicity
  - common arrhythmias seen with hypokalemia: ventricular fibrillation, ventricular tachycardia

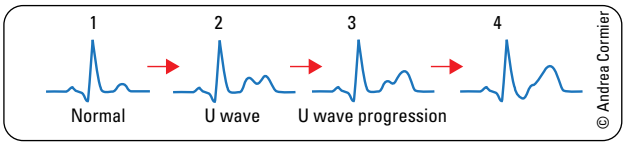



**Figure 6. ECG changes in hypokalemia**

## Approach to Hypokalemia

1. emergency measures if $K^+$ <2.5 mEq/L: obtain ECG; if potentially life threatening, begin treatment immediately
2. rule out transcellular shifts of $K^+$ as cause of hypokalemia
3. assess contribution of dietary $K^+$ intake
4. spot urine K:Cr (should be less than 1.5 mEq/mmol in setting of hypokalemia)
   - if <1.5 mEq/mmol consider GI loss
   - if >1.5 mEq/mmol consider a renal loss
5. consider 24 h $K^+$ excretion
6. if renal $K^+$ loss, check BP and acid-base status
7. may also assess plasma renin and aldosterone levels, serum [$Mg^{2+}$]

- Hypokalemia often accompanied by metabolic alkalosis
- Potassium leaves cells, replaced by $H^+$
- Kidney tubular cells see high $H^+$, think acidosis, and increase ammonium synthesis and excretion
- Increase in bicarbonate generation

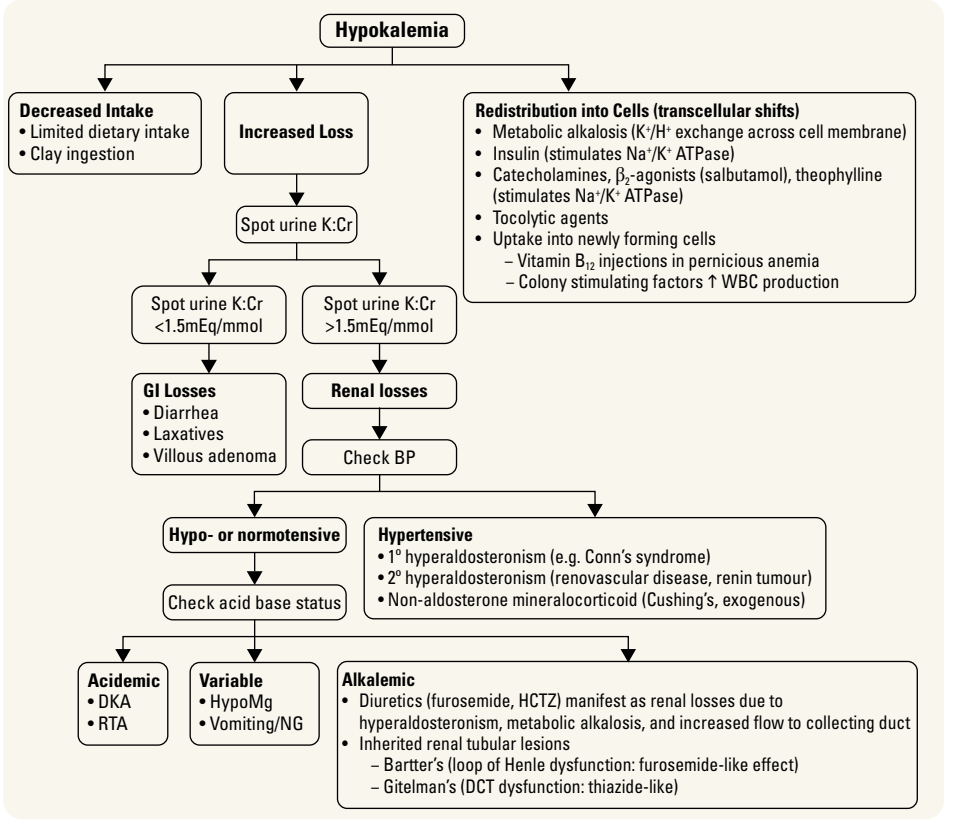



**Figure 7. Approach to hypokalemia**

## Treatment

- treat underlying cause
- if true $K^+$ deficit, potassium repletion
  - oral sources – food, tablets (K-Dur™), KCl liquid solutions (preferable route if the patient tolerates PO medications)
  - IV – usually KCl in saline solutions, avoid dextrose solutions (may exacerbate hypokalemia via insulin release)
- max 40 mmol/L via peripheral vein, 60 mmol/L via central vein, max infusion 20 mmol/h
- $K^+$-sparing diuretics (triamterene, amiloride, spironolactone) can prevent renal $K^+$ loss
- restore $Mg^{2+}$ before correcting $K^+$
- if urine output and renal function are impaired, correct with extreme caution
- risk of hyperkalemia with potassium replacement especially high in elderly, diabetics, and patients with decreased renal function
- use ACE inhibitor or ARB for CHF (reduces angiotensin II action and therefore reduces aldosterone production)
- beware of excessive potassium repletion, especially if transcellular shift caused hypokalemia

# Hyperkalemia

- serum [$K^+$] >5.0 mEq/L

## Signs and Symptoms

- usually asymptomatic but may develop nausea, palpitations, muscle weakness, muscle stiffness, paresthesias, areflexia, ascending paralysis, and hypoventilation
- impaired renal ammoniagenesis and metabolic acidosis
- ECG changes and cardiotoxicity (do not correlate well with serum [$K^+$])
- peaked and narrow T waves
- decreased amplitude and eventual loss of P waves
- prolonged PR interval
- widening of QRS and eventual merging with T wave (sine-wave pattern)
- AV block
- ventricular fibrillation, asystole

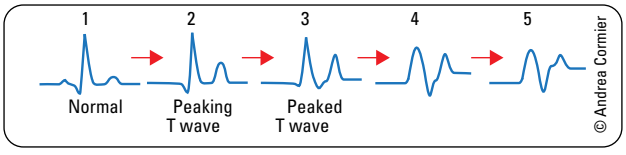



**Figure 8. ECG changes in hyperkalemia**

### Table 6. Causes of Hyperkalemia

| Factitious | Increased Intake | Transcellular Shift | Decreased Excretion |
|---|---|---|---|
| Sample hemolysis*<br>Sample taken from vein where IV KCl is running<br>Prolonged use of tourniquet<br>Leukocytosis (extreme)<br>Thrombocytosis** (extreme) | Diet<br>KCl tabs<br>IV KCl<br>Salt substitute | Intravascular hemolysis<br>Rhabdomyolysis<br>Tumour lysis syndrome<br>Insulin deficiency<br>Acidemia<br>Drugs<br>β-blockers<br>Digitalis overdose (blocks $Na^+/K^+$ ATPase)<br>Succinylcholine | Decreased GFR<br>Renal failure<br>Low effective circulating volume<br>NSAIDs in renal insufficiency<br>Normal GFR but hypoaldosteronism |

*Most common **Usually when blood specimen has been sitting out long before being analyzed

### Table 7. Causes of Hyperkalemia with Normal GFR

| Decreased Aldosterone Stimulus (low renin, low aldosterone) | Decreased Aldosterone Production (normal renin, low aldosterone) | Aldosterone Resistance (decreased tubular response) |
|---|---|---|
| Associated with diabetic nephropathy, NSAIDs, chronic interstitial nephritis, HIV | Adrenal insufficiency of any cause (e.g. Addison's disease, AIDS, metastatic cancer)<br>ACEI<br>Angiotensin II receptor blockers<br>Heparin<br>Congenital adrenal hyperplasia with 21-hydroxylase deficiency | $K^+$-sparing diuretics<br>Spironolactone<br>Amiloride<br>Triamterene<br>Renal tubulointerstitial disease |

## Approach to Hyperkalemia

1. emergency measures: obtain ECG, if life threatening begin treatment immediately
2. rule out factitious hyperkalemia; repeat blood test
3. hold exogenous $K^+$ (PO and IV) and any medications that are $K^+$ retaining (e.g. RAAS inhibitors (ACEI, ARBs), aldosterone antagonists, non-selective beta-blockers (propranolol/labetalol)) or affect $K^+$ excretion (i.e. NSAIDs)
4. assess potential causes of transcellular shift
5. estimate GFR (calculate CrCl using Cockcroft-Gault)

In patients with DM and increased [$K^+$] and hyperglycemia, often just giving insulin to restore euglycemia is sufficient to correct the hyperkalemia

## Treatment

- acute therapy is warranted if ECG changes are present or if patient is symptomatic regardless of [$K^+$]
- tailor therapy to severity of increase in [$K^+$] and ECG changes
  - [$K^+$] <6.5 and normal ECG
    - treat underlying cause, stop $K^+$ intake, increase the loss of $K^+$ via urine and/or GI tract
  - [$K^+$] between 6.5 and 7.0, no ECG changes: add insulin to above regimen
  - [$K^+$] >7.0 and/or ECG changes: first priority is to protect the heart, add calcium gluconate to above

**Treatment of Hyperkalemia**

**C BIG K DROP**
**C** – Calcium gluconate
**BIG** – β-agonist, Bicarbonate, Insulin, Glucose
**K** – Kayexalate®
**DROP** – Diuretics, Dialysis

### 1. Stabilize Myocardium

- calcium gluconate 1-2 amps (10 mL of 10% solution) IV
- antagonizes the membrane action of hyperkalemia, protects cardiac conduction system, no effect on serum [$K^+$]
- onset within minutes, lasts 30-60 min (may require repeat doses during treatment course of hyperkalemia)

**2. Shift $K^+$ into Cells**
- regular insulin (Insulin R) 10-20 units IV, with 1-2 amp D50W (give D50W before insulin)
  - onset of action 15-30 min, lasts 1-2 h
  - monitor capillary blood glucose q1h because of risk of hypoglycemia
  - can repeat every 4-6 h
  - caution giving D50W before insulin if hyperkalemia is severe as it can cause a serious arrhythmia
- NaHCO3 1-3 ampules (given as 3 ampules of 7.5% or 8.4% NaHCO3 in 1 L D5W)
  - onset of action 15-30 min, transient effect, drives $K^+$ into cells in exchange for H+
  - more effective if patient has metabolic acidosis
- β2-agonist (Ventolin®) in nebulized form (dose = 2 cc or 10 mg inhaled) or 0.5 mg IV
  - onset of action 30-90 min, stimulates $Na^+/K^+$ ATPase
  - caution if patient has heart disease as may result in tachycardia

**3. Enhance $K^+$ Removal from Body**
- via urine (preferred approach)
  - furosemide (≥40 mg IV), may need IV NS to avoid hypovolemia
  - fludrocortisone (synthetic mineralocorticoid) if suspecting aldosterone deficiency
- via GI (if renal function is severely impaired)
  - cation-exchange resins: calcium resonium or sodium polystyrene sulfonate (Kayexalate®) (which is prescribed in conjunction with sorbitol)
- Kayexalate® in combination with sorbitol should NOT be used as long-term therapy for chronic hyperkalemia as it is not very effective at lowering $K^+$ levels and may also lead to the development of colonic necrosis
- lactulose or sorbitol PO to avoid constipation (must ensure that patient has a bowel movement after resin is administered - main benefit may be the diarrhea caused by lactulose)
- dialysis (renal failure, life threatening hyperkalemia unresponsive to therapy)

**Management of Patients with Acute Hyperkalemia**
CMAJ 2010;182:1631-1635
**Purpose**: To review the evidence supporting different treatment options for acute hyperkalemia.
**Study**: Systematic review of updated research since 2005 Cochrane review, search 2003-2009 inclusive.
**Results**: Four new articles continued to support the acute usage of insulin and beta-agonists for shifting, and hemodialysis for elimination in severe and refractory hyperkalemia. One small randomized study comparing resins to laxatives was identified by the reviewers. It found no significant difference in serum potassium of the two groups in the 4 hours following administration. Study design was reportedly flawed; the resin group as a whole had lower initial serum concentration than the laxative control group.
**Conclusion**: Standard of care continues to include insulin, beta-agonists, and hemodialysis. There is no clear evidence supporting the use of resins, such as Kayexalate, for the acute management of hyperkalemia. Furthermore, prior studies have shown that resin usage can result in bowel obstruction and bowel necrosis.

# Hyperphosphatemia

## Definition
- serum phosphate >1.45 mmol/L
  - phosphate binds to serum calcium to create insoluble precipitates in soft tissues and blood vessels, thereby resulting in hypocalcemia
  - hypocalcemia subsequently triggers the development of secondary hyperparathyroidism in patients with advanced CKD on dialysis

## Etiology
- typically results from decreased renal excretion of phosphate

**Table 8. Etiology of Hyperphosphatemia**

| Increased Phosphate Load | Reduced Renal Clearance | Pseudohyperphosphatemia |
|---|---|---|
| GI intake (rectal enema, GI bleeding)<br>IV phosphate load (K-Phos®, blood transfusion)<br>Endogenous phosphate (tumour lysis syndrome, rhabdomyolysis, hemolysis, lactic and ketoacidosis) | Acute/chronic renal failure<br>Hypoparathyroidism<br>Acromegaly<br>Tumour calcinosis (ability of kidney to specifically clear phosphate is defective) | Hyperglobulinemia<br>Hyperlipidemia<br>Hyperbilirubinemia |

## Clinical Features
- non-specific, include ectopic calcification in soft tissues and vessels, renal osteodystrophy
  - symptoms consistent with hypocalcemia (e.g. tetany)

## Treatment
- acute: IV saline, hemodialysis if symptomatic;
- chronic: low $PO_4^{3-}$ diet, phosphate binders (e.g. $CaCO_3$ or lanthanum carbonate or sevelamer with meals)

# Hypophosphatemia

## Definition
- serum phosphate <0.80 mmol/L

## Etiology
- acute hypophosphatemia often caused by intracellular shifts of phosphate superimposed on chronic phosphate depletion
- chronic hypophosphatemia often caused by decreased renal phosphate reabsorption
- severe chronic hypophosphatemia often caused by chronic starvation or malabsorption (e.g. in patients with alcoholism) or chronic use of phosphate binders (e.g. patients with CKD)

Symptoms usually present when phosphate <0.32 mmol/L (1.0 mg/dL)
Treat asymptomatic patients if phosphate <0.32 mmol/L

Severe burns can cause hypophosphatemia due to $PO_4^{3-}$ losses through the skin

**Table 9. Etiology of Hypophosphatemia**

| Inadequate Intake | Renal Losses | Excessive Skeletal Mineralization | Shift into Intracellular Fluid |
|---|---|---|---|
| Starvation<br>Malabsorption (diarrhea, steatorrhea)<br>Antacid use<br>Alcoholism | Hyperparathyroidism<br>Diuretics<br>X-linked or autosomal dominant hypophosphatemic Rickets<br>Fanconi syndrome<br>Multiple myeloma<br>Early post-kidney transplant | Osteoblastic metastases<br>Post parathyroidectomy (referred to as 'hungry bone syndrome') | Recovery from metabolic acidosis<br>Respiratory alkalosis<br>Starvation refeeding (stimulated by insulin) |

### Clinical Features
- instability of cell membranes leading to hemolytic anemia or rhabdomyolysis
- MSK weakness, respiratory depression, low cardiac output/CHF from weakened cardiac muscles – symptoms arise due to low ATP production
- neurological symptoms: irritability, encephalopathy, seizures, coma
- hematologic symptoms: hemolytic anemia, decreased release of oxygen from hemoglobin, impaired leukocyte and platelet function (leading to worsening infections/defective clotting)

### Treatment
- initiate when serum [$PO_4^{3-}$] <0.64 mmol/L and symptomatic, or <0.32 mmol/L if asymptomatic
- treat underlying cause
  - Oral $PO_4^{3-}$: 2-4 g/d divided bid-qid (start at 1 g/d to minimize diarrhea), encourage $PO_4^{3-}$ rich diet
  - IV $PO_4^{3-}$: only for severely symptomatic patients or inability to tolerate oral therapy

## Hypermagnesemia

### Definition
- serum magnesium >1.05 mmol/L

### Etiology
- AKI/CRF
- $Mg^{2+}$-containing antacids or enemas
- IV administration of large doses of $MgSO_4$ (e.g. see Obstetrics, *Preeclampsia* OB24)

### Clinical Features
- rarely symptomatic
- drowsiness, hyporeflexia, respiratory depression, heart block, cardiac arrest, hypotension

### Treatment
- discontinue $Mg^{2+}$-containing products
- 10% calcium gluconate 10-20 mL IV ($Mg^{2+}$-antagonist) for acute reversal of magnesium toxicity
- hemodialysis if renal failure, consider peritoneal dialysis in setting of hemodynamic compromise

## Hypomagnesemia



You will be unable to correct hypokalemia or hypocalcemia without first supplementing magnesium if patient is hypomagnesemic

### Definition
- serum magnesium <0.70 mmol/L

### Etiology

| GI losses | Excess renal loss |
|---|---|
| Starvation/malabsorption | 2° hyperaldosteronism due to cirrhosis and CHF |
| Vomiting/diarrhea | Hyperglycemia |
| Alcoholism | Hypokalemia |
| Acute pancreatitis | Hypercalcemia |
| | Loop and thiazide-type diuretics |
| | Nephrotoxic medications |
| | Proton-pump inhibitors |
| | Early post-renal transplant |

### Clinical Features
- tremors, nausea and vomiting, lethargy/weakness, seizures, paresis, Chvostek and Trousseau signs, ECG changes (widened QRS, prolonged PR, T-wave abnormalities), and arrhythmias including Torsades de Pointes

### Treatment
- treat underlying cause
- encourage increased dietary intake e.g. fruits
- oral $Mg^{2+}$ salts unless patient has seizures or other severe symptoms
- $Mg^{2+}$ IM/IV; cellular uptake of $Mg^{2+}$ is slow, therefore repletion requires sustained correction
- discontinue diuretics
  - in patients requiring diuretics, use a $K^+$-sparing diuretic to minimize magnesuria

# Acid-Base Disorders

- acid-base homeostasis influences protein function and can critically affect tissue and organ function with consequences to cardiovascular, respiratory, metabolic, and CNS function
- see Respirology, R6 for more information on respiratory acidosis/alkalosis
- normal concentration of $HCO_3^-$ = 24 mEq/L (range: 22-30 mEq/L)
- normal $pCO_2$ = 40 mmHg (range: 36-44 mmHg)
- each acid-base disorder has an appropriate compensation
  - inadequate compensation or overcompensation can indicate the presence of a second acid-base disorder (e.g. in metabolic acidosis, inadequate compensation means there is also respiratory acidosis; overcompensation means there is also respiratory alkalosis)

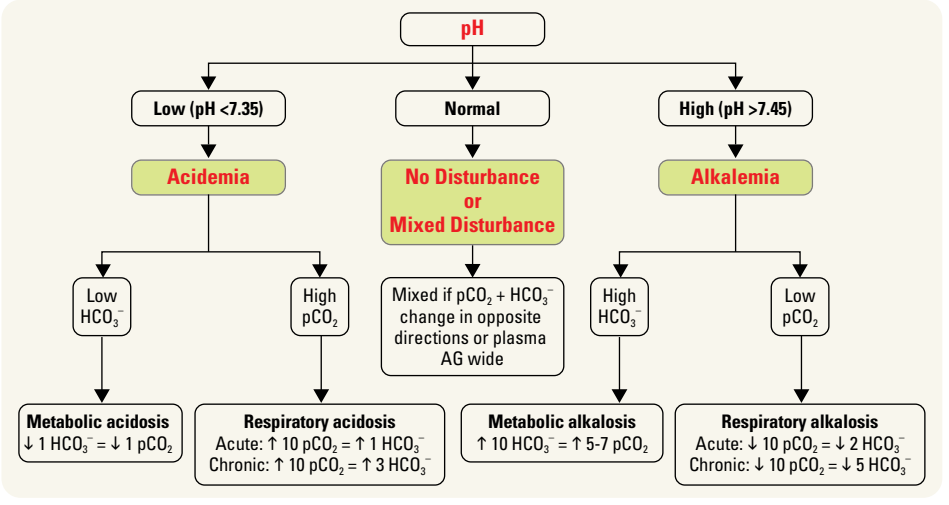



**Figure 9. Approach to acid-base disorders**

## Approach

**1. Identify the Primary Disturbance**
- respiratory acidosis, metabolic acidosis, respiratory alkalosis, metabolic alkalosis

**2. Evaluate Compensation. If compensation is not appropriate, second acid-base disorder is likely present**
- compensation occurs in the same direction as the primary disturbance

**3. Calculate Plasma AG**
- AG = $[Na^+]$ – ($[HCO_3^-]$ + $[Cl^-]$)
- baseline = 12, normal range 10-14 mEq/L
- AG can be altered by plasma albumin level: for each 10 g/L fall in albumin, lower baseline AG by 3 mEq/L (e.g. if plasma [albumin] = 20 g/L, expect AG = 6 mEq/L)

**4. If AG elevated, compare increase in AG with decrease in $HCO_3^-$**
- if increase in AG < decrease in $HCO_3^-$, there is a coexisting non-AG metabolic acidosis
- if increase in AG > decrease in $HCO_3^-$, there is a coexisting metabolic alkalosis

**5. Calculate Osmolar Gap**
- osmolar gap = measured osmolality – calculated osmolality
  - calculated osmolality = (2 x $[Na^+]$) + [urea] + [glucose] (all units are in mmol/L)
  - normal osmolar gap <10
  - If OG >10, consider: methanol poisoning, ethylene glycol poisoning, or another cause of acidosis plus ethanol ingestion

**Causes of Increased Osmolar Gap**
- Methanol
- Ethylene glycol
- Ethanol
- Polyethelene glycol
- Mannitol
- Sorbitol

**Useful Equations**
- AG = $[Na^+]$ - $[Cl^-]$ - $[HCO^{3-}]$ (normal range = 10-14 mEq/L)
- Osmolar Gap = measured serum osmolality – calculated osmolality (normal <10 mEq/L) – "Two Salts and a Sticky BUN"
- Calculated Osmolality = 2$[Na^+]$ + [Urea] + [Glucose] (+1.25[Ethanol])

# Metabolic Acidosis

## Etiology and Pathophysiology

**1. Increased AG Metabolic Acidosis (4 types)**

1. lactic acidosis (2 types)
   - L-lactic acid
     - type A: due to tissue hypoperfusion (any cause of shock), ischemic bowel, profound hypoxemia
     - type B: non-hypoxic – multiple causes; the most common is failure to metabolize normally produced lactic acid in the liver due to severe liver disease; other causes include: excessive alcohol intake, thiamine deficiency, metformin accumulation (metformin interferes with electron transport chain), certain anti-retrovirals, large tumours, mitochondrial myopathies
   - D-lactic acid: rare syndrome characterized by episodes of encephalopathy and metabolic acidosis
     - occurs in the setting of carbohydrate malabsorption (e.g. short bowel syndrome), colonic bacteria metabolize carbohydrate load into D-lactic acid, diminished colonic motility, and impaired D-lactate metabolism

**Causes of Increased AG Metabolic Acidosis**

**MUDPILES CAT**
**M**ethanol
**U**remia
**D**iabetic ketoacidosis
**P**araldehyde
**I**sopropyl alcohol/**I**ron/**I**buprofen/
**I**ndomethacin
**L**actic acidosis
**E**thylene glycol
**S**alicylates
**C**yanide and **C**arbon monoxide
**A**lcoholic ketoacidosis
**T**oluene

2. ketoacidosis
   - diabetic
   - starvation
   - alcoholic (decreased carbohydrate intake and vomiting)
3. toxins
   - methanol (toxic to brain and retina, can cause blindness and brain death): metabolized to formic acid
   - ethylene glycol (toxic to brain and kidneys): metabolized to oxalic acid (envelope shaped crystals in urine) and multiple other acids
   - salicylate (e.g. ASA) overdose: causes acidosis due to salicylic acid, and also accumulation of lactic acid (salicylate at toxic levels impairs electron transport chain) and ketoacid (salicylate activates fat breakdown)
4. advanced renal failure (e.g. serum Cr increased at least 5x above baseline – a very low GFR causes anion retention, and renal disease leads to impaired bicarbonate production)

**2. Normal AG Metabolic Acidosis (Hyperchloremic Acidosis) (involves increased bicarbonate excretion that is replaced with Cl)**
- diarrhea ($HCO_3^-$ loss from GI tract)
- RTA
  - type I RTA (distal): inability to secrete $H^+$ in collecting duct, leading to impaired excretion of ammonium into urine
  - type II RTA (proximal): impaired $HCO_3^-$ reabsorption
  - type III RTA: combination of Types I and II and is extremely rare
  - type IV RTA: defective ammoniagenesis due to decreased aldosterone, hyporesponsiveness to aldosterone, or hyperkalemia
- to help distinguish renal causes from non-renal causes, use Urine AG = $(Na^+ + K^+) - Cl^-$
- calculation establishes the presence or absence of unmeasured positive ions (e.g. $NH_4^+$) in urine
  - if UAG <0, suggests adequate $NH_4^+$ excretion in urine (likely nonrenal cause: diarrhea)
  - if UAG >0, suggests problem is lack of $NH_4^+$ in urine (e.g. distal RTA)

**Causes of Non-AG Metabolic Acidosis**
**HARDUP**
**H**yperalimentation
**A**cetazolamide
**R**TA*
**D**iarrhea*
**U**reteroenteric fistula
**P**ancreaticoduodenal fistula
*Most common

### Treatment of Metabolic Acidosis
1. treat underlying cause:
   - fluid resuscitation and insulin for DKA
   - restore tissue perfusion for Type A lactic acidosis
   - ethanol/fomepizole ± dialysis for methanol or ethylene glycol poisoning
   - alkaline diuresis ± dialysis if ASA overdose
2. correct coexisting disorders of $K^+$ (see *Hyperkalemia*, NP13)
3. consider treatment with exogenous alkali (e.g. $NaHCO_3$) if:
   - severe reduction in $[HCO_3^-]$ e.g. <8 mmol/L, especially with very low pH (<7)
   - no metabolizable anion (e.g. salicylate, formate, oxalate, or sulphate); note that lactate and ketoacid anions can be metabolized to $HCO_3^-$

- note: risks of sodium bicarbonate therapy
  - hypokalemia: causes $K^+$ to shift into cells (correct $K^+$ deficit first)
  - ECF volume overload: $Na^+$ load given with $NaHCO_3$, can exacerbate pulmonary edema
  - overshoot alkalosis: abrupt, poorly tolerated transition from overly aggressive alkali loading, partial conversion of accumulated organic anions to $HCO_3^-$, and persisting hyperventilation

**3 Clinical Scenarios that Produce a Mixed Disorder with Near Normal pH**
(e.g. increased AG metabolic acidosis + respiratory alkalosis)
- Cirrhosis
- ASA overdose
- Sepsis

# Metabolic Alkalosis

### Pathophysiology
- requires initiating event and maintenance factors
- precipitating factors
  - GI (vomiting, NG tube) or renal loss of $H^+$
  - exogenous alkali (oral or parenteral administration), milk alkali syndrome
  - diuretics (contraction alkalosis): decreased excretion of $HCO_3^-$, decreased ECF volume, therefore increased $[HCO_3^-]$
  - post-hypercapnia: renal compensation for respiratory acidosis is $HCO_3^-$ retention, rapid correction of respiratory disorder results in transient excess of $HCO_3^-$
- maintenance factors
  - volume depletion: reduced GFR and increased proximal reabsorption of $NaHCO_3^-$ and increased aldosterone
  - hyperaldosteronism (1° or 2°): distal $Na^+$ reabsorption in exchange for $K^+$ and $H^+$ excretion leads to metabolic alkalosis; aldosterone also promotes hypokalemia
  - hypokalemia: transcellular $K^+/H^+$ exchange, stimulus for ammoniagenesis and $HCO_3^-$ generation

### Evaluate Compensation (identify co-existing respiratory acid-base disorders)
- hypoventilation (an upper limit to compensation exists – breathing cannot be stopped)

### Treatment
- treat underlying cause
- correct underlying disease, replenish $K^+$ and $Mg^{2+}$ deficits, and possibly $K^+$-sparing diuretic
- saline sensitive metabolic alkalosis (most common)
  - volume repletion ± carbonic anhydrase inhibitor (e.g. acetazolamide) to facilitate loss of $HCO_3^-$ in urine
- saline resistant metabolic alkalosis
  - remove source of aldosterone or glucocorticoid ± spironolactone

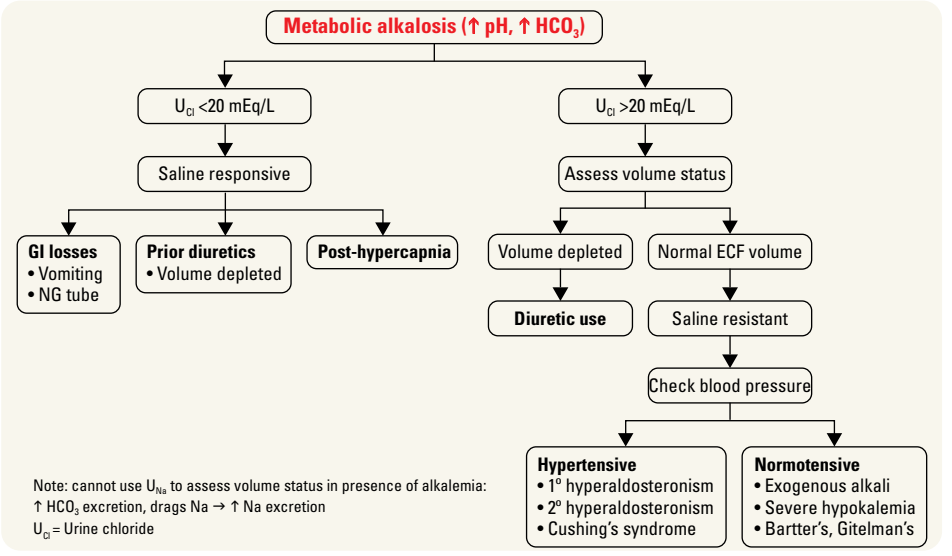



**Figure 10. Approach to metabolic alkalosis**

# Polyuria

## Definition
- output greater than 3 L/d. Distinguish from urinary frequency, where urination occurs multiple times per day but the total volume over 24 h is <3 L

## Etiology
- drugs (most commonly diuretics)
- excessive caffeine, alcohol intake
- increased water intake (psychogenic polydipsia, IV fluids)
- uncontrolled diabetes mellitus (osmotic diuresis)
- neurological: diabetes insipidus (central and peripheral), cerebral salt-wasting syndrome
- genitourinary: post-obstructive diuresis, cystitis/UTI

## Clinical Features
- must distinguish between true polyuria and urinary frequency
- look for sources of external fluid intake (IV fluids, tube feedings)
- assess for neurological changes (stroke, trauma, post-operative) (for central diabetes insipidus)
- assess for drugs that may cause nephrogenic diabetes insipidus (e.g. lithium)
- abrupt onset suggests central diabetes insipidus

## Investigation Findings
- hypernatremia suggests free water loss secondary to diabetes insipidus
  - hyponatremia suggests free water intake secondary to polydipsia
  - measure serum electrolyte/osmolality and urine osmolality after water deprivation test, see *Diabetes Insipidus*, NP11 for complete workup for diabetes insipidus

## Treatment
- addressed to etiology

# Acute Kidney Injury

## Definition
- abrupt decline in renal function leading to increased nitrogenous waste products normally excreted by the kidney
- formerly known as acute renal failure

The 2 most common causes of acute kidney injury in hospitalized patients are prerenal azotemia and ATN; remember that prerenal failure can lead to ATN

**Table 10. Classification of Acute Kidney Injury**

| CRITERIA | RIFLE | AKIN | KDIGO |
|---|---|---|---|
| **Serum Creatinine** | Increased 2-3 times baseline | Increase of ≥26.4 μmol/L or increase by >50%, within 48 h | Increase of ≥26.4 μmol/L within 48 h or increase by >50% within 7 d |
| **GFR** | Decreased >50% | N/A | N/A |
| **Urine Output** | <0.5 mL/kg/h for >12 h | <0.5 mL/kg/h for >6 h | <0.5 mL/kg/h for >6 h |

## Clinical Feature
- azotemia (increased BUN, Cr)
- abnormal urine volume: formally <0.5 ml/kg/h for >6 h but can manifest as anuria, oliguria, or polyuria

# Approach to AKI

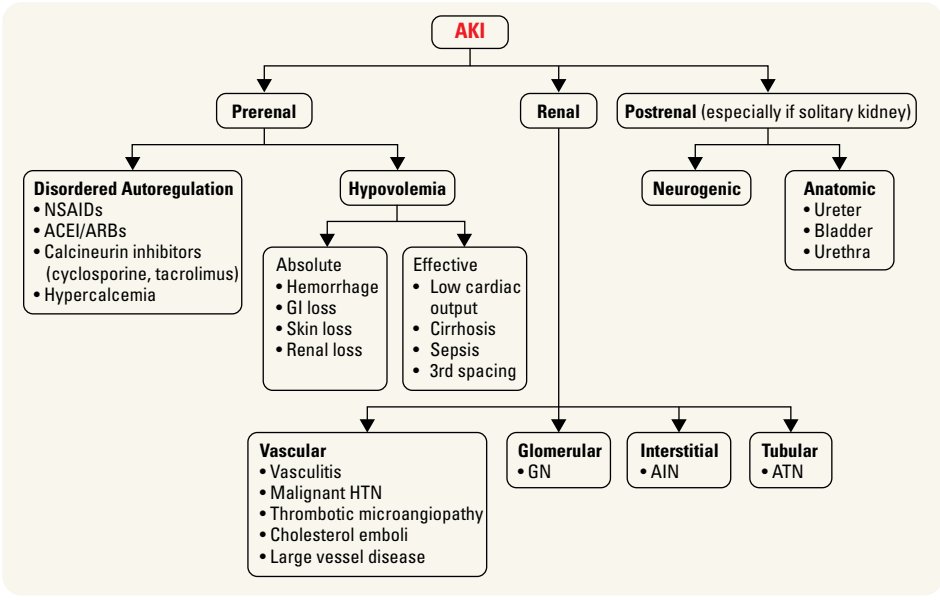



**Figure 11. Approach to AKI**

**Clues to Prerenal Etiology**
- Clinical: Decreased BP, increased HR, and orthostatic HR and BP changes
- Increased [urea] >> Increased [Cr]
- Urine [$Na^+$] <10-20 mmol/L
- Urine osmolality >500 mOsm/kg
- Fractional excretion of $Na^+$ <1%

**Clues to Renal Etiology**
- Appropriate clinical context
- Urinalysis positive for casts:
  Pigmented granular – ATN
  WBC – AIN
  RBC – GN
- Systemic features, anemia, thrombocytopenia, HTN, mild-moderate ECF volume overload

**Clues to Postrenal Etiology**
- Known solitary kidney
- Older man
- Recent retroperitoneal surgery
- Anuria
- Palpable bladder
- Ultrasound shows hydronephrosis

## Investigations
- blood work: CBC, electrolytes, Cr, urea (think prerenal if increase in urea is relatively greater than increase in Cr), $Ca^{2+}$, $PO_4^{3-}$
- urine dipstick: albumin, hemoglobin, WBC's, others: glucose, pH, urobilinogen, specific gravity
- urine volume, C&S, R&M: sediment, casts, crystals
- urinary indices: electrolytes, osmolality
- Foley catheterization (rule out bladder outlet obstruction)
- fluid challenge (e.g. fluid bolus to rule out most prerenal causes)
- imaging: abdomen U/S (assess kidney size, hydronephrosis, postrenal obstruction)
- indications for renal biopsy
  - diagnosis is not certain
  - prerenal azotemia or ATN is unlikely
  - oliguria persists >2-4 d
  - RPGN, signs of significant glomerular disease (proteinuria, RBC casts) despite normal kidney size/echogenicity

**Differentiating Prerenal from ATN**

| | Prerenal | ATN |
|---|---|---|
| Urinalysis | Normal | RBC, pigmented granular casts |
| Urine [$Na^+$] | <20 | >20 mEq/L |
| Urine[$Na^+$]/[Cr] | <20 | >20 |
| Urine osmolality | >500 | <350 mOsm/kg$H_2O$ |
| FeNa | <1% | >1% |

## Treatment
1. preliminary measures
   - prerenal
     - correct prerenal factors: optimize volume status and cardiac performance using fluids that will stay in the plasma subcompartment (NS, albumin, blood/plasma), hold ACEI/ARB (gently rehydrate when needed, e.g. CHF) and NSAIDs
   - renal
     - address reversible renal causes: discontinue nephrotoxic drugs, treat infection, and optimize electrolytes
     - correct ECF volume, supportive care, consider corticosteroid or immunosuppressive therapy
   - postrenal
     - consider obstruction: structural (stones, strictures) vs. functional (neuropathy)
     - for obstruction to cause AKI, must have functional solitary kidney or obstruction affecting both kidneys
     - treat with Foley catheter insertion, indwelling bladder catheter, nephrostomy, stenting
2. treat complications
   - fluid overload
     - NaCl restriction
     - high dose loop diuretics
     - hyperkalemia (see *Hyperkalemia*, NP13)
     - adjust dosages of medications cleared by kidney (e.g. amiodarone, digoxin, cyclosporin, tacrolimus, some antibiotics, and chemotherapeutic agents)
   - dialysis
3. definitive therapy depends on etiology

Avoid NSAIDs in patients with diarrhea, heart failure or renal failure

Renal transplant is not a therapy for AKI

**Drugs Implicated in Prerenal Azotemia**
- Diuretics
- NSAIDs
- ACEI/ARBs

## Prognosis
- high morbidity and mortality in patients with sustained AKI and multi-organ failure

# Parenchymal Kidney Diseases

## Glomerular Diseases

### HISTOLOGICAL TERMS OF GLOMERULAR CHANGES

#### Extent of Changes

- histological term describing the number of glomeruli affected in a given condition:
  - diffuse: majority of glomeruli abnormal
  - focal: some glomeruli affected
- histological term describing the extent to which individual glomeruli are affected in a given condition
  - global: entire glomerulus abnormal
  - segmental: only part of the glomerulus abnormal

#### Types of Changes

- proliferation: hyperplasia of one of the glomerular cell types (mesangial, endothelial, parietal epithelial), with or without inflammatory cell infiltration
  - crescent formation: parietal epithelial cell proliferation and mononuclear cell infiltration form crescent-shape in Bowman's space
- membranous changes: capillary wall thickening due to immune deposits or alterations in basement membrane

### CLINICAL FEATURE OF GLOMERULAR DISEASE

#### Important Points to Remember

- glomerular diseases have diverse clinical features including hematuria, proteinuria, HTN, edema, and decreased GFR
  - each glomerulopathy presents as one of four major glomerular syndromes (these are NOT diagnoses)
    1. asymptomatic urinary abnormalities
       - proteinuria
       - hematuria
    2. nephritic syndrome
       - acute GN
       - rapidly progressive GN
    3. nephrotic syndrome
    4. ESRD
- glomerulopathies can be caused by a primary disease or can occur secondary to a systemic disease
- some glomerulopathies can present as more than one syndrome at different times

#### The Nephritic-Nephrotic Spectrum

- glomerular pathology can present with a clinical picture anywhere on a spectrum with pure nephritic and pure nephrotic syndromes at the extremes

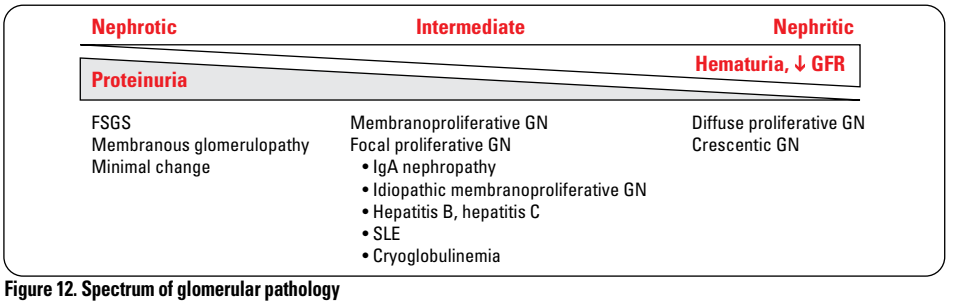



**Figure 12. Spectrum of glomerular pathology**

### PROTEINURIA

- hallmark of nephrotic syndromes
- composition of normal urine protein: albumin, lower molecular proteins (such as immunoglobulin light chain), or proteins secreted by the tubular epithelial cells (e.g. Tamm-Horsfall mucoprotein)
- 24 h urine protein: gold standard to assess degree of proteinuria
- spot/random urine ACR: used to screen for diabetic nephropathy and proteinuric renal disease
- microalbuminuria: ACR ≥2.0 mg/mmol
  - marker of vascular endothelial function
  - an important prognostic marker for chronic kidney disease (see *Diabetes*, NP31)
  - microalbuminuria is the earliest sign of diabetic nephropathy
- composition of normal total urine protein
- upper limit of normal daily excretion of total protein is 150 mg/d
- upper limit of normal daily excretion of albumin is 30 mg/d
- the other normally excreted proteins are either filtered low molecular weight proteins (such as immunoglobulin light chains or β-2 microglobulin) or proteins secreted by the tubular epithelial cells (e.g. Tamm-Horsfall mucoprotein)

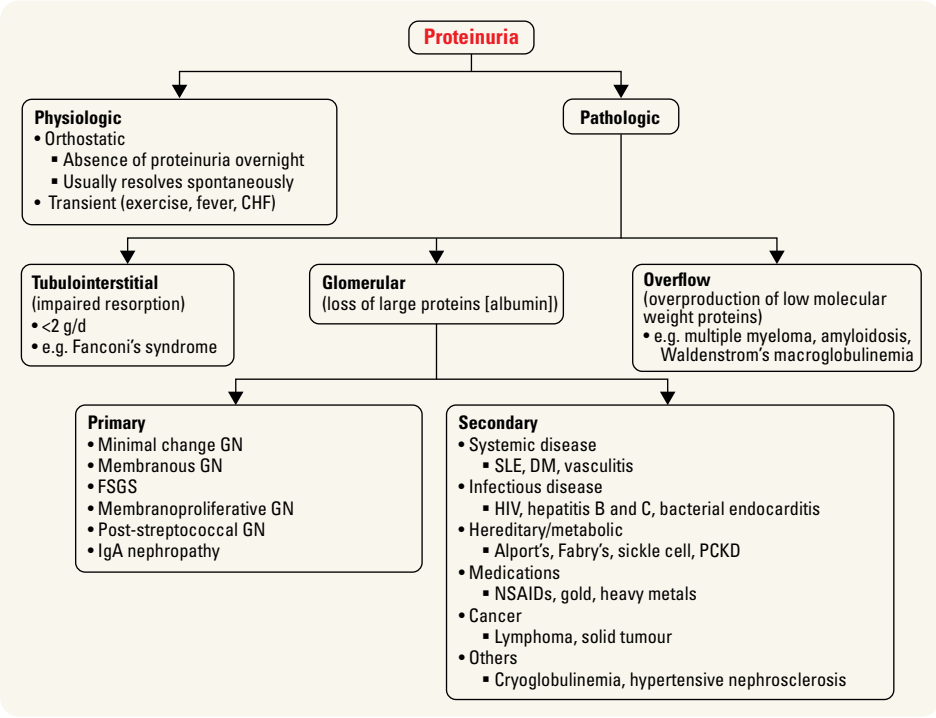



**Figure 13. Classification of proteinuria**

**Table 11. Daily Excretion of Protein**

| Daily Excretion | Stage of Nephropathy | ACR | PCR |
|---|---|---|---|
| <150 mg total protein (and <30 mg albumin) | Normal | <2.0 mg/mmol | <15 mg/mmol |
| 30-300 mg albumin | Microalbuminuria | >2.0 mg/mmol | |
| >3500 mg total protein/1.73m$^2$ body surface area | Nephrotic range proteinuria | >220 mg/mmol | >300 mg/mmol |
| Variable amount of proteinuria | Can be seen with glomerular disease | | |
| Up to 2000 mg per d | Possible tubular disease because of failure to reabsorb filtered proteins | | |

**Pathologic Proteinuria**

**Tubulointerstitial**
- Normally low molecular weight proteins (<60 kDa) pass through glomerular filtration barrier and are reabsorbed in proximal tubule
- Proximal tubule dysfunction causes impaired reabsorption and increased excretion of low molecular weight proteins
- Albumin (>60 kDa) is not affected; thus, edema is partly secondary to salt and water retention

**Glomerular**
- Normally, the filtration barrier is selectively permeable to size (<60 kDa) and charge (repels negative particles); thus, albumin is filtered to a very limited extent through a normal glomerulus
- Damage to any component of the glomerular filtration barrier results in loss of albumin and other high molecular weight proteins; thus, edema is secondary to hypoalbuminemia (low oncotic pressure), but also due to enhanced renal tubular reabsorption of filtered sodium and water (possibly due to filtered proteins stimulating the action of cortical collecting duct epithelial sodium channel)

**Overflow**
- Increased production of low molecular weight proteins which exceeds the reabsorptive capacity of the proximal tubule
- Plasma cell dyscrasias produce light chain Ig (multiple myeloma, Waldenstrom's macroglobulinemia, monoclonal gammopathy of undetermined significance)

### Investigations
- urea, creatinine, ACR, PCR
- urine R&M, C&S
- further workup (if degree of proteinuria >0.5 g/d, casts, and/or hematuria)
  - CBC, glucose, electrolytes, 24 h urine protein, and Cr
  - urine and serum immunoelectrophoresis, abdominal/pelvic U/S
  - serology: ANA, RF, p-ANCA (MPO), c-ANCA (PR3), C3, C4, Hep B, Hep C, HIV, ASOT
- consider urology consult and possible cystoscopy if not clearly a nephrologic source for hematuria or if >50 yr of age

# Glomerular Syndromes

## 1. ASYMPTOMATIC URINARY ABNORMALITIES

### Clinical/Lab Features
- often have rapid decline in GFR, anemia, elevated inflammatory markers, ECF volume replete or mildly overloaded
- proteinuria (usually <2 g/d) and/or microscopic or macroscopic hematuria
  - isolated proteinuria
    - can be postural
    - occasionally can signal beginning of more serious GN (e.g. FSGS, IgA nephropathy, amyloid, diabetic nephropathy)
  - hematuria with or without proteinuria
    - IgA nephropathy (Berger's disease): most common type of primary glomerular disease worldwide, frequently presents after viral upper respiratory tract infection
      - more common in Caucasian and Asian populations, and in the 2nd and 3rd decades of life
      - may be associated with cirrhosis, HIV infection, celiac disease
      - potential treatment includes: RAAS blockers if proteinuria, steroids, and steroid sparing agents (azathioprine, cyclophosphamide, mycophenolate mofetil, and biologics such as rituximab)

- hereditary nephritis (Alport Syndrome – Type IV collagen mutation): X-linked nephritis often associated with sensorineural hearing loss; proteinuria <2 g/d
- thin basement membrane disease: usually autosomal dominant, without proteinuria; benign
- benign recurrent hematuria: hematuria associated with febrile illness, exercise, or immunization; a diagnosis of exclusion after other possibilities are ruled out

## 2. NEPHRITIC SYNDROME

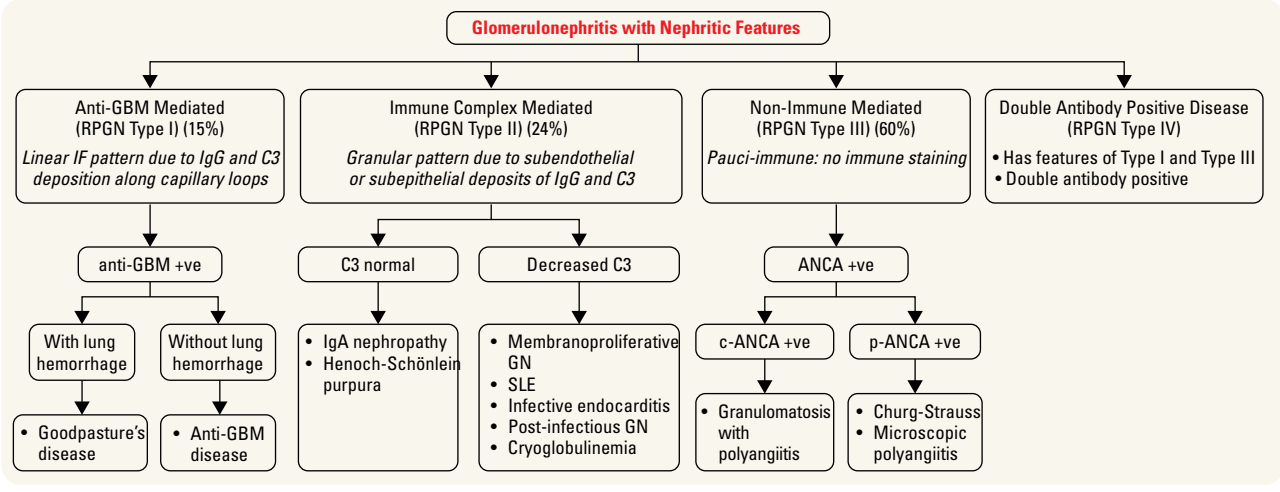



**Figure 14. Approach to nephritic syndrome**

### ACUTE NEPHRITIC SYNDROME

- a subset of nephritic syndrome in which the clinical course occurs over days
- etiology can be divided into low and normal complement levels
- frequently immune-mediated, with Ig and C3 deposits found in GBM; but may be pauci-immune and caused by an ANCA vasculitis

#### Clinical/Lab Features

- proteinuria (but <3.5 g/1.73 $m^2$/d)
- hematuria (microscopic or macroscopic)
- azotemia (increased Cr and urea)
- RBC casts and/or dysmorphic RBCs in urine
- HTN (due to salt and water retention)
- peripheral edema/puffy eyes

#### Treatment

- depends on etiology
- pulse steroid therapy and other immunosuppression (steroid sparing agents such as azathioprine and cyclophosphamide, mycophenolate mofetil, and biologics such as rituximab), BP control (with RAAS agents, plasma exchange), monitoring for progression to end stage renal disease

**Interventions for Renal Vasculitis in Adults**
Cochrane DB Syst Rev 2015;CD003232
**Objective**: To assess benefits and harms of any intervention used for the treatment of renal vasculitis in adults.
**Methods**: RCTs in Cochrane Kidney and Transplant Specialized Register investigating any intervention for the treatment of renal vasculitis in adults.
**Conclusions**: Plasma exchange was effective in patients with severe AKI secondary to vasculitis. Pulse cyclophosphamide resulted in an increased risk of relapse (compared to continuous oral) but required reduced dose. Rituximab and mycophenolate mofetil were comparable in efficacy to cyclophosphamide. Azathioprine, methotrexate and leflunomide were effective as maintenance therapy.

### RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

- a subset of nephritic syndrome in which the clinical course occurs over weeks to months
- clinical diagnosis, not histopathological
- any type of GN can present as RPGN (except minimal change disease)
- additional etiologies seen only as RPGN: anti-GBM disease and granulomatosis with polyangiitis (previously called Wegener's granulomatosis)
- crescentic GN (identified by pathology) is frequently seen in RPGN resulting from proliferation of parietal epithelial cells and is the most aggressive form of glomerular disease

#### Clinical/Lab Features

- fibrous crescents typically present on renal histopathology
- RBC casts and/or dysmorphic RBCs in urine
- classified by immunofluorescence staining
- Type I: anti-GBM mediated (15% of cases)
- Type II: immune complex mediated (24% of cases)
- Type III: non-immune mediated (60% of cases)
- Type IV: double antibody positive

#### Treatment and Prognosis

- treatment: underlying cause for postinfectious; corticosteroids and cyclophosphamide or other cytotoxic agent and plasmapheresis in management of cases such as anti-GBM Ab
- prognosis: 50% recovery with early treatment, depends on underlying cause

## 3. NEPHROTIC SYNDROME

### Definition
- distinct constellation of clinical and laboratory features of renal disease defined by the presence of heavy proteinuria (protein excretion greater than 3.5 g/24 h), hypoalbuminemia (less than 3 g/dL), and peripheral edema

### Clinical/Lab Features
- heavy proteinuria (>3.5 g/1.73 $m^2$/d)
- hypoalbuminemia
- edema
- hyperlipidemia (elevated LDL cholesterol), lipiduria (fatty casts and oval fat bodies on microscopy)
- hypercoagulable state (due to antithrombin III, Protein C, and Protein S urinary losses)
- patient may report frothy urine
- glomerular pathology on renal biopsy (nephrotic syndrome is always caused by glomerular pathology)
- minimal change disease (or minimal lesion disease or nil disease) – e.g. glomeruli appear normal on light microscopy
  - membranous glomerulopathy
  - focal segmental glomerulosclerosis (FSGS)
  - membranoproliferative GN
  - nodular amyloidosis
- each can be idiopathic or secondary to a systemic disease or drug (sirolimus can cause proteinuria without obvious glomerular pathology; sirolimus rarely causes nephrotic syndrome)

**Table 12. Nephrotic Syndrome**

| | Minimal Change | Membranous Glomerulopathy | Focal Segmental Glomerulosclerosis | Membranoproliferative Glomerulonephritis | Nodular Glomerulosclerosis |
|---|---|---|---|---|---|
| **Secondary Causes** | Hodgkin's lymphoma | HBV, SLE, solid tumours (lung, breast, GI) | Reflux nephropathy, HIV, HBV, obesity, sickle cell disease | HCV, malaria, SLE, leukemia, lymphoma, shunt nephritis | DM, amyloidosis |
| **Drug Causes** | NSAIDs | Gold, penicillamine | Heroin | | |
| **Therapy** | Steroids | Reduce BP, ACEI, steroids | Steroids, ACEI/ARB for proteinuria | Aspirin®, ACEI, dipyridamole (Persantine®) – controversial | Treat underlying cause |

Note: the most common secondary causes are diabetes mellitus and amyloidosis

## INVESTIGATIONS FOR GLOMERULAR DISEASE
- blood work
  - first presentation: electrolytes, Cr, urea, albumin, fasting lipids, ACR
  - determining etiology: CBC, ESR, serum immunoelectrophoresis (for amyloidosis or multiple myeloma), C3, C4, ANA, p-ANCA, c-ANCA, cryoglobulins, HBV and HCV serology, ASOT (anti-streptolysin titres), VDRL, HIV, anti-glomerular basement membrane antibodies (anti-GBM)
- urinalysis: RBCs, WBCs, casts, protein
- 24 h urine for protein and CrCl
- radiology
  - CXR (infiltrates, CHF, pleural effusion)
  - renal U/S
- renal biopsy (percutaneous or open) if heavy proteinuria or renal insufficiency and cause is not obviously diabetic nephropathy
- urine immunoelectrophoresis
  - for Bence-Jones protein if proteinuria present
- renal pathology (light microscopy, immunofluorescence, electron microscope)
- serum protein electrophoresis (SPEP)

## SECONDARY CAUSES OF GLOMERULAR DISEASE

### Amyloidosis
- nodular deposits of amyloid in mesangium, usually related to amyloid light chain (AL)
- presents as nephrotic range proteinuria with progressive renal insufficiency
- can be primary or secondary
- secondary causes: multiple myeloma, TB, rheumatoid arthritis, malignancy

### Lupus
- see Rheumatology, RH11
- lupus nephritis can present as any of the glomerular syndromes
- nephrotic syndrome with an active sediment is most common presentation
- GN caused by immune complex deposition in capillary loops and mesangium with resulting renal injury
- serum complement, ANA, anti-DNA levels are usually low during periods of active renal disease
- children and males with SLE are more likely to develop nephritis

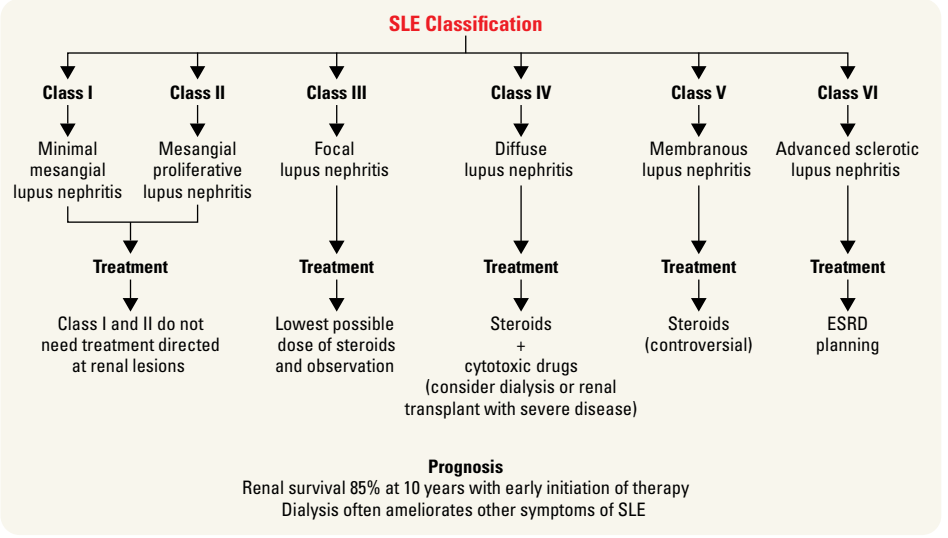



**Figure 15. International Society of Nephrology/Renal Pathology Society classification of lupus nephritis 2003**

## Henoch-Schönlein Purpura

- seen more commonly in children
- purpura on buttocks and legs, abdominal pain, arthralgia, and fever
- IgA and C3 staining of mesangium
- usually benign, self-limiting course, 10% progress to CKD

## ANCA-Associated Vasculitis

- c-ANCA most commonly associated with the clinical picture of granulomatosis with polyangiitis
- p-ANCA most commonly associated with the clinical picture of microscopic polyangiitis
- focal segmental necrotizing RPGN with no immune staining
- may be indolent or fulminant in progression
- vasculitis and granulomas rarely seen on renal biopsy
- treatment typically involves cyclophosphamide and prednisone

## Cryoglobulinemia

- cryoglobulins: monoclonal IgM and polyclonal IgG which precipitate at reduced temperatures
- presents as purpura, fever, Raynaud's phenomenon, and arthralgias
- at least 50% of patients have hepatitis C
- renal disease seen in 40% of patients (isolated proteinuria/hematuria progressing to nephritic syndrome)
- most patients have decreased serum complement (C4 initially)
- treat hepatitis C, plasmapheresis
- overall prognosis: 75% renal recovery

## Shunt Nephritis

- immune-complex mediated nephritis associated with chronically infected ventriculoatrial shunts inserted for treatment of hydrocephalus
- commonly *S. epidermidis* is the cause
- presents as acute nephritic syndrome with decreased serum complement
- nephrotic range proteinuria in 25% of patients
- treat by removing shunt and administering appropriate antibiotics; can consider a ventriculoperitoneal shunt

## HIV-Associated Renal Disease

1. direct nephrotoxic effect of HIV infection, anti-retroviral drugs (e.g. tenofovir, indinavir), and other drugs used to treat HIV-associated infections
2. HIV-associated nephropathy
   - histology: focal and segmental glomerular collapse with mesangial sclerosis; "collapsing FSGS"
   - tubular cystic dilation and tubulo-reticular inclusions
   - clinical features: predominant in African American men, heavy proteinuria, progressive renal insufficiency (Apo-L-1 risk genotypes)
   - prognosis: kidney failure within 1 yr without treatment
   - therapy: short-term, high dose steroids, ACEI, HAART

**EULAR Recommendations for the Management of Systemic Lupus Erythematosus (SLE)**
Ann Rheum Dis 2008;67:195-205
**Lupus Nephritis Recommendations**
**Monitoring**: Renal biopsy, urine sediment analysis, proteinuria, and kidney function may have independent predictive ability for clinical outcome in therapy of lupus nephritis but need to be interpreted in conjunction. Changes in immunological tests (anti-dsDNA, serum C3) have limited ability to predict response to treatment and may be used only as supplemental information.
**Treatment**: In patients with proliferative lupus nephritis, glucocorticoids in combination with immunosuppressive agents are effective against progression to end-stage renal disease. Long-term efficacy has been demonstrated only for cyclophosphamide-based regimens, which are associated with considerable adverse effects. In short- and medium-term trials, mycophenolate mofetil has demonstrated at least similar efficacy compared with pulse cyclophosphamide and a more favourable toxicity profile. Failure to respond by 6 mo should evoke discussions for intensification of therapy. Flares following remission are not uncommon and require diligent follow-up.
**End-Stage Renal Disease**: Dialysis and transplantation in SLE have long-term patient and graft-survival rates comparable with those observed in non-diabetic non-SLE patients, with transplantation being the method of choice.

### Infective Endocarditis
- manifests as mild form of acute nephritic syndrome with decreased serum complement
- *S. aureus* is most common infecting agent
- treatment with appropriate antibiotics usually resolves GN

### Hepatitis B
- can result in membranous nephropathy, polyarteritis nodosa, membranoproliferative GN

### Hepatitis C
- can result in membranous nephropathy, cryoglobulinemia, and membranoproliferative GN

### Syphilis
- can result in membranous GN

### END STAGE RENAL DISEASE
- see *End Stage Renal Disease*, NP37

# Tubulointerstitial Disease

### TUBULOINTERSTITIAL NEPHRITIS



IgA nephropathy is the most common type of primary glomular disease worldwide

### Definition
- cellular infiltrates affecting primarily the renal interstitium and tubular cells
- functional tubule defects are disproportionately greater than the decrease in GFR
- classified as acute or chronic

### Signs and Symptoms
- manifestation of disease depends on site of tubule affected

1. proximal tubule (e.g. multiple myeloma, heavy metals)
   - Fanconi syndrome: decreased reabsorption in proximal tubule causing glycosuria, aminoaciduria, phosphaturia, hyperuricosuria
   - proximal RTA (decreased bicarbonate absorption): Type II RTA
2. distal tubule (e.g. amyloidosis, obstruction)
   - distal RTA (Type I RTA), usually hypokalemic
   - $Na^+$-wasting nephropathy
   - ± hyperkalemia leading to Type IV RTA (where reduced renal bicarbonate production is caused by hyperkalemia)
3. collecting duct (e.g. sickle cell anemia, analgesics, PCKD)
   - urinary concentrating defect leading to mild nephrogenic DI
   - polyuria



**Features of Nephritic Syndrome**

**PHAROH**
**P**roteinuria
**H**ematuria
**A**zotemia
**R**BC casts
**O**liguria
**H**TN



**Presentation of Nephrotic Syndrome**
**HELP**
**H**ypoalbuminemia
**E**dema
**L**ipid abnormalities
**P**roteinuria

### 1. ACUTE TUBULOINTERSTITIAL NEPHRITIS

### Definition
- rapid (d to wk) decline in renal function
- 10-20% of all AKI

### Etiology
- hypersensitivity
  1. antibiotics: β-lactams, sulfonamides, rifampin, quinolones, cephalosporins, fluoroquinolones
  2. other: NSAIDs, allopurinol, furosemide, thiazides, triamterene, PPIs, acyclovir, phenytoin, cimetidine
- infections
  - bacterial pyelonephritis, Streptococcus, brucellosis, Legionella, CMV, EBV, toxoplasmosis, leptospirosis, HIV, Mycoplasma
- immune
  - SLE, acute allograft rejection, Sjögren's syndrome, sarcoidosis, mixed essential cryoglobulinemia
- idiopathic (renal-ocular syndrome – acute tubulointerstitial nephritis plus uveitis)

### Pathophysiology
- acute inflammatory cell infiltrates into renal interstitium

### Clinical Features
- AKI
- if hypersensitivity reaction (common with antibiotics): may see fever, skin rash, arthralgia, serum sickness-like syndrome (particularly rifampin)
- if pyelonephritis: flank pain and costovertebral angle (CVA) tenderness
- if drug reaction, AKI usually occurs 7-10 d after exposure
- other signs and symptoms based on underlying etiology
- HTN and edema are uncommon

### Findings
- urine
  - mild, non-nephrotic range proteinuria and microscopic hematuria
  - sterile pyuria, WBC casts
  - eosinophils if AIN
- blood work
  - increased Cr and urea
  - eosinophilia if drug reaction (high negative predictive value, common in β-lactam reactions)
  - normal AG metabolic acidosis (RTA)
  - hypophosphatemia, hypo- OR hyperkalemia, hyponatremia
- gallium scan often shows intense signal due to inflammatory infiltrate
- renal biopsy definitive – shows interstitial infiltrates and edema on biopsy

### Treatment
- treat underlying cause (e.g. stop offending medications, antibiotics if pyelonephritis)
- corticosteroids (may be indicated in allergic or immune disease)

### Prognosis
- recovery within 2 wk if underlying insult can be eliminated
- the longer the patient is in renal failure, the less likely they will have a full renal recovery

## 2. CHRONIC TUBULOINTERSTITIAL NEPHRITIS

### Definition
- characterized by slowly progressive renal failure, moderate proteinuria, and signs of abnormal tubule function

### Etiology
- persistence or progression of acute TIN
  - may also involve concurrent glomerular involvement
- urinary tract obstruction: most important cause of chronic TIN (tumours, stones, bladder outlet obstruction, vesicoureteral reflux)
- chronic pyelonephritis due to vesicoureteral reflux or UTI with obstruction
- nephrotoxins
  - exogenous
    - analgesics: NSAIDs (common), acetaminophen
    - cisplatin, lithium, cyclosporine, tacrolimus
    - heavy metals (lead, cadmium, copper, lithium, mercury, arsenic)
    - Chinese herbs (aristolochic acid)
  - endogenous
    - hypercalcemia, hypokalemia, oxalate, uric acid
- vascular disease: ischemic nephrosclerosis, atheroembolic disease
- malignancies: multiple myeloma, lymphoma
- granulomatous: TB, sarcoidosis, granulomatosis with polyangiitis
- immune: SLE, Sjögren's, cryoglobulinemia, anti-GBM disease, amyloidosis, renal graft rejection, vasculitis
- hereditary: cystic diseases of the kidney, sickle cell disease
- others: radiation, Balkan (endemic) nephropathy

### Pathophysiology
- fibrosis of interstitium with atrophy of tubules, mononuclear cell inflammation

### Signs and Symptoms
- dependent on underlying etiology

### Findings
- normal AG metabolic acidosis
- hyperkalemia (out of proportion to degree of renal insufficiency)
- polyuria, nocturia
- partial or complete Fanconi's syndrome
- progressive renal failure with azotemia and uremia
- urine: mild proteinuria, few RBCs and WBCs, no RBC casts
- U/S: shrunken kidneys with irregular contours (differentiates acute from chronic etiology)

### Treatment
- stop offending agent or treat underlying disease
- supportive measures: correct metabolic disorders ($Ca^{2+}$, $PO_4^{3-}$) and anemia

## 3. ACUTE TUBULAR NECROSIS

### Definition
- abrupt and sustained decline in GFR within minutes to days after ischemic/nephrotoxic insult
- GFR reduced (this serves the purpose of avoiding life-threatening urinary loss of fluid and electrolytes from non-functioning tubules)

### Etiology

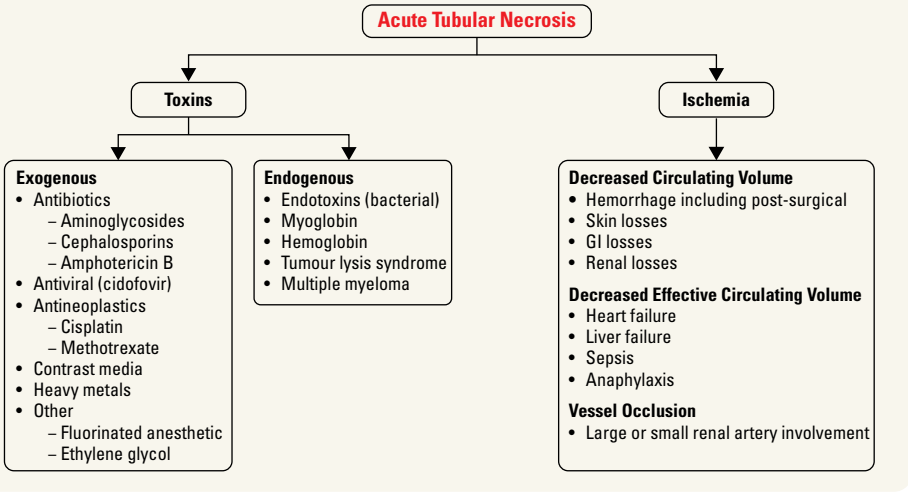



**Figure 16. Etiology of ATN**

**Effectiveness of Prevention Strategies for Contrast-Induced Nephropathy: A Systematic Review and Meta-Analysis**
Ann Intern Med 2016;164(6):406-16
**Objective**: To evaluate the comparative effectiveness of interventions to reduce contrast-induced nephropathy in adults receiving contrast media.
**Methods**: Meta-analysis of RCTs N-acetylcysteine, sodium bicarbonate, statins, or ascorbic acid that used IV or intra-arterial contrast media.
**Results**: Low dose N-acetylcysteine+IV saline vs. IV saline (RR 0.75, 95% CI 0.63-0.89). N-acetylcysteine+IV saline vs. IV saline (RR 0.69, 95% CI 0.58-0.84). Statins+N-acetylcysteine+IV saline vs. N-acetylcysteine+IV saline (RR 0.52, 95% CI 0.29-0.93). Clinically important, but not statistically significant, reductions were observed in sodium bicarbonate vs. IV saline, statins+IV saline vs. IV saline, and ascorbic acid vs. IV saline.
**Conclusions**: Greatest reduction in contrast-induced nephropathy was seen with N-acetylcysteine plus IV saline and statins plus N-acetylcysteine plus IV saline.

### Clinical Feature
- typically presents as an abrupt rise in urea and Cr after a hypotensive episode, sepsis, rhabdomyolysis, or administration of nephrotoxic drug
  - pre-renal AKI can eventually progress to ATN
  - usually asymptomatic, patient may experience oliguria in severe cases
- physical exam may show signs of true or effective ECF volume depletion
- most common cause of non-prerenal AKI in hospitalized patients
- urine: high $FE_{Na^+}$, pigmented-granular casts

### Risk Factors
- pre-existing chronic kidney disease, pre-existing cardiovascular disease, ECF volume depletion, multiple renal insults

### Complications
- hyperkalemia: can occur rapidly and cause serious arrhythmias
- metabolic acidosis, decreased $Ca^{2+}$, increased $PO_4^{3-}$, hypoalbuminemia

### Investigations
- blood work: CBC, electrolytes, Cr, urea, $Ca^{2+}$, $PO_4^{3-}$, blood gases
- urine: R&M, electrolytes, osmolality, microscopic urinalysis searching for pigmented granular casts
- ECG
- abdominal U/S
- rule out other causes of prerenal/postrenal azotemia and intrinsic AKI (GN, AIN, vasculitis)
  - IV fluid challenge will not increase urine output or normalize serum creatinine in ATN, helps to differentiate ATN from pre-renal AKI
  - if diagnosis is uncertain, biopsy

### Treatment
- largely supportive once underlying problem is corrected
- consideration for early dialysis in severe/rapidly progressing cases to prevent uremic syndrome (the STARRT-AKI study addressing this is ongoing)

### Prevention
- correct fluid balance before surgical procedures
- for patients with chronic renal disease requiring radiographic contrast:
  - isotonic saline
  - avoid giving diuretics, NSAIDS, ACEI, cyclosporine on morning of procedure if possible
- use renal-adjusted doses of nephrotoxic drugs in patients with renal insufficiency
- use low dose non-ionic, iso- or low-osmolal contrast agents

# Vascular Diseases of the Kidney

## LARGE VESSEL DISEASE

**Table 13. Summary of Vascular Diseases**

| Large Vessel Disease | Medium Vessel Disease | Small Vessel Disease |
|---|---|---|
| Acute renal artery occlusion (infarct) | Kawasaki disease | Hypertensive nephrosclerosis |
| Renal artery stenosis (ischemia) | Polyarteritis nodosa | Atheroembolic renal disease |
| Renal vein thrombosis | | Thrombotic microangiopathy |
| | | Scleroderma |
| | | Calcineurin inhibitor nephropathy |
| | | Hemolytic Uremic Syndrome (HUS) |

## 1. RENAL INFARCTION (ACUTE RENAL ARTERY OCCLUSION)

- important, potentially reversible cause of renal failure

### Etiology

- abdominal trauma, surgery, embolism, vasculitis, extra-renal compression, hypercoagulable state, aortic dissection
- kidney transplant recipients more vulnerable

### Signs and Symptoms (depend on presence of collateral circulation)

- fever, N/V, flank pain
- leukocytosis, elevated AST, ALP
- marked elevated LDH (LDH >4x upper limit of normal with minimal elevations in AST/ALT strongly suggestive)
- acute onset HTN (activation of RAAS) or sudden worsening of long-standing HTN
- renal dysfunction, e.g. elevated Cr (if bilateral, or solitary functioning kidney)

### Investigations

- renal arteriography (more reliable but risk of atheroembolic renal disease)
- contrast-enhanced CT or MR angiography, duplex Doppler studies (operator dependent)

### Treatment

- prompt localization of occlusion and restoration of blood flow
- anticoagulation, thrombolysis, percutaneous angioplasty or clot extraction, surgical thrombectomy
- medical therapy in the long-term to reduce risk (e.g. antihypertensives)

## 2. ISCHEMIC RENAL DISEASE (RENAL ARTERY STENOSIS)

- chronic renal impairment secondary to hemodynamically significant renal artery stenosis or microvascular disease
- significant cause of ESRD: 15% in patients >50 yr (higher prevalence if significant vascular disease)
- usually associated with large vessel disease elsewhere
- causes of renal artery stenosis
  - atherosclerotic plaques (90%): proximal 1/3 renal artery, usually males >55 yr, smokers
  - fibromuscular dysplasia (10%): distal 2/3 renal artery or segmental branches, usually young females (typical onset <30 yr)
- when there is decreased RBF, GFR is dependent on angiotensin II-induced efferent arteriolar constriction which raises the FF (GFR/RBF)
- most common cause of secondary HTN ("renovascular HTN"), 1-2% of all hypertensive patients
  - **etiology**
    - decreased renal perfusion of one or both kidneys leads to increased renin release and subsequent angiotensin production
    - increased angiotensin raises blood pressure in two ways
      1. causes generalized arteriolar constriction
      2. release of aldosterone increases Na+ and water retention
  - elevated blood pressure can in turn lead to further damage of kidneys and worsening HTN

### Risk Factors

- >50 yr
- smoking
- other atherosclerotic disease (dyslipidemia, DM, diffuse atherosclerosis)



**Treatment of Hypertension in Association with Renovascular Disease**
Can J Cardiol 2017;33(5):557-76
**Guidelines:**
1. Recommend medical management as renal angioplasty and stenting offers no benefit over optimal medical therapy alone.
2. In patients with uncontrolled HTN resistant to maximally tolerated pharmacotherapy, progressive renal function loss and acute pulmonary edema, renal artery angioplasty and stenting for atherosclerotic hemodynamically significant stenosis could be considered.
Patients with confirmed renal fibromuscular dysplasia should be referred to HTN specialist and considered for revascularization.

### Signs and Symptoms
- severe/refractory HTN and/or hypertensive crises, with negative family history of HTN
- asymmetric renal size
- epigastric or flank bruits
- spontaneous hypokalemia (renin activation in under-perfused kidney)
- increasing Cr with ACEI/ARB
- flash pulmonary edema with normal LV function

### Investigations
- must establish presence of renal artery stenosis and prove it is responsible for renal dysfunction
- duplex Doppler U/S (kidney size, blood flow): good screening test (operator dependent)
- digital subtraction angiography (risk of contrast nephropathy)
- CT or MR angiography (effective noninvasive tests to establish presence of stenosis, for MR avoid gadolinium contrast if eGFR <30 mL/min because of risk of systemic dermal fibrosis)
- ACEI renography (e.g. captopril renal scan)
- renal arteriography (gold standard)

### Treatment
- surgical: percutaneous angioplasty ± stent, surgical revascularization, occasionally surgical bypass
- medical: BP lowering medications (ACEI is drug of choice if unilateral renal artery disease but contraindicated if bilateral renal artery disease)
- little or no benefit if therapy is late (e.g. kidney is already shrunken), however, therapy can be considered to save the opposite kidney if normal

## 3. RENAL VEIN THROMBOSIS

### Etiology
- hypercoagulable states (e.g. nephrotic syndrome, especially membranous), ECF volume depletion, extrinsic compression of renal vein, significant trauma, malignancy (e.g. RCC), sickle cell disease
- clinical features determined by rapidity of occlusion and formation of collateral circulation

### Signs and Symptoms
- acute: N/V, flank pain, hematuria, elevated plasma LDH, ± rise in Cr, sudden rise in proteinuria
- chronic: PE (typical first presenting symptom), increasing proteinuria and/or tubule dysfunction

### Investigations
- renal venography (gold standard), CT or MR angiography, duplex Doppler U/S

### Treatment
- thrombolytic therapy ± percutaneous thrombectomy for acute renal vein thrombosis
- anticoagulation with heparin then warfarin (1 yr or indefinitely, depending on risk factors)

## MEDIUM VESSEL DISEASE

## 1. KAWASAKI DISEASE
- see Pediatrics, P88

## 2. POLYARTERITIS NODOSA
- see Rheumatology, RH20
- kidneys most commonly involved organ
- heterogenous impact on renal function
- pathologically can cause glomerular ischemia which manifests as mild proteinuria and hypertension

## SMALL VESSEL DISEASE

## 1. HYPERTENSIVE NEPHROSCLEROSIS
- see *Hypertension*, NP35

## 2. ATHEROEMBOLIC RENAL DISEASE
- progressive renal insufficiency due to embolic obstruction of small- and medium-sized renal vessels by atheromatous emboli
- spontaneous or after renal artery manipulation (surgery, angiography, percutaneous angioplasty)
- anticoagulants and thrombolytics interfere with ulcerated plaque healing and can worsen disease
- **investigations**
  - eosinophilia, eosinophiluria, and hypocomplementemia
  - renal biopsy: needle-shaped cholesterol clefts (due to tissue-processing artifacts) with surrounding tissue reaction in small-/medium-sized vessels



**Stenting and Medical Therapy for Atherosclerotic Renal Artery Stenosis**
NEJM 2014;370:13-22
**Study**: Multicentre, unblinded RCT, median follow-up of 43 mo.
**Patients**: 947 patients with atherosclerotic renal-artery stenosis who also have significant systolic HTN or CKD.
**Intervention**: Percutaneous revascularization (stenting) with medical therapy (statins, ARB, calcium channel blockers, HCTZ, and BP control) versus medical therapy alone.
**Outcomes**: Occurrence of adverse CV or renal event (composite of death from CV or renal cause, MI, stroke, hospitalization for CHF, progressive renal insufficiency, or need for renal replacement therapy) and all-cause mortality.
**Results**: No significant difference in primary composite end point between participants who received stenting or those on medical therapy alone. No significant differences between the treatment groups in the rates of the individual components of the primary end point or in all-cause mortality.
**Conclusion**: Renal artery stenting did not confer a significant benefit with respect to the prevention of clinical events when added to comprehensive, multifactorial medical therapy in people with atherosclerotic renal artery stenosis and HTN or CKD.

- **treatment**
  - no effective treatment; avoid angiographic and surgical procedures in patients with diffuse atherosclerosis, medical therapy for concomitant cardiovascular disease
- **prognosis**: poor overall, at least one third will develop ESRD

### 3. THROMBOTIC MICROANGIOPATHY
- see Hematology, H22
- etiologies include the spectrum of TTP-HUS, DIC, severe preeclampsia, drug-induced, complement mediated, metabolism-mediated, and coagulation-mediated
- the enzyme ADAMTS13 is reduced in TTP, and ADAMTS13 autoantibody are useful for diagnosing TTP
- events leading to HUS often begin with the ingestion of Shiga toxin-producing *E. coli*
- renal involvement more common in HUS than TTP
- renal involvement characterized by fibrin thrombi in glomerular capillary loops ± arterioles
- **treatment**
  - depends on cause
  - supportive therapy
  - TTP-HUS: plasma exchange, corticosteroids (splenectomy and rituximab if refractory)
- avoid platelet transfusions and ASA

### 4. CALCINEURIN INHIBITOR NEPHROPATHY
- secondary to the use of cyclosporine and tacrolimus
- causes both acute reversible and chronic, largely irreversible nephrotoxicity
- major cause of kidney failure in other solid organ transplants (e.g. heart)
- acute: due to afferent and efferent glomerular capillary constriction leading to decreased GFR (tubular vacuolization)
  - prerenal azotemia
  - treatment: calcium channel blockers or prostaglandin analogs, reduce dose of cyclosporine or switch to another immunosuppressive drug
- chronic: result of obliterative arteriolopathy causing interstitial nephritis and CKD (striped fibrosis), less frequent now due to lower doses of calcineurin inhibitors



**Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation (ELITE-Symphony Trial)**
NEJM 2007;257:2562-2575
**Study**: Multicentre, RCT with 12 mo follow-up.
**Patients**: 1645 patients scheduled to receive a single organ kidney transplant.
Intervention: Mycophenolate mofetil, corticosteroids, and either: 1) standard dose cyclosporine; 2) low dose cyclosporine with daclizumab induction; 3) low dose tacrolimus with daclizumab induction; 4) low dose sirolimus with daclizumab induction.
**Primary Outcome**: Estimated Cockcroft-Gault GFR 12 mo after transplantation.
**Results**: The tacrolimus arm showed significantly higher eGFR at 12 mo compared to all other arms (65.4 mL/min vs. 57.1, 59.4, 56.7 for arms 1, 2, 4 respectively, $p \leq 0.001$). The tacrolimus arm also showed decreased rates of acute rejection at 6 mo and 12 mo vs. all arms ($p<0.001$), improved allograft survival against standard dose cyclosporine and sirolimus, and decreased treatment failure against all other arms. There was no difference in overall patient survival between groups. Sirolimus had the highest incidence of lymphoceles, delayed wound healing, and serious adverse events; tacrolimus had significantly higher rates of new-onset DM; and cyclosporine regimes had the lowest incidence of diarrhea but highest opportunistic infection rates.
**Conclusion**: Immunosuppression regiments using low dose tacrolimus and daclizumab induction decrease nephrotoxicity while maintaining therapeutic immunosuppression in renal transplant patients.

## Analgesic Nephropathies

### 1. Vasomotor AKI
- clinically: develop prerenal azotemia within a few days of starting NSAID
- normally prostaglandins vasodilate afferent renal arteriole to maintain blood flow
- NSAIDs act by blocking cyclooxygenase enzyme, thereby preventing prostaglandin synthesis and causing renal ischemia
- more common in elderly, underlying renal disease, hypovolemia (diuretics, CHF, cirrhosis, nephrotic syndrome)
- treatment: discontinue NSAID, dialysis rarely needed

### 2. Acute Interstitial Nephritis
- fenoprofen (60%), ibuprofen, naproxen
- may be associated with minimal change glomerulopathy and nephrotic range proteinuria
- resolves eventually with discontinuation of NSAID, may require interval dialysis
- short-term high dose steroids (1 mg/kg/d of prednisone) may hasten recovery

### 3. Chronic Interstitial Nephritis
- due to excessive consumption of antipyretics (phenacetin or acetaminophen) in combination with NSAIDs
- seen in patients who also have emotional stress, psychiatric symptoms, and GI disturbance
- papillary necrosis
  - gross hematuria, flank pain, declining renal function
  - calyceal filling defect seen with IVP – "ring sign"
- increased risk of transitional cell carcinoma of renal pelvis
- good prognosis if discontinue analgesics

### 4. Acute Tubular Necrosis
- can be caused by acetaminophen
  - incidence of renal dysfunction is related to the severity of acetaminophen ingestion
- vascular endothelial damage can also occur
- both direct toxicity and ischemia contribute to the tubular damage
- renal function spontaneously returns to baseline within 1-4 wk
- dialysis may be required during the acute episode of ingestion

### 5. Other Effects of NSAIDs
- sodium retention (2° to reduced GFR)
- hyperkalemia, HTN (2° to hyporeninemic hypoaldosteronism)
- excess water retention (2° to loss of antagonistic effect of prostaglandins on ADH)

# Systemic Disease with Renal Manifestation

## Diabetes

- diabetic nephropathy: presence of microalbuminuria or overt nephropathy (e.g. macroalbuminuria, impaired GFR) in patients with DM who lack indicators of other renal diseases
- most common cause of end-stage renal failure in North America
- 50% of patients with diabetes will develop nephropathy
- greater burden in Indigenous communities
  - in Indigenous youth diagnosed with diabetes before age 20, risk of developing end-stage renal disease was 2.59 times higher compared to non-First Nations people with diabetes
  - 55.1% of First Nations individuals diagnosed with diabetes had chronic kidney disease
- at diagnosis up to 30% of patients with type 2 DM have albuminuria (75% microalbuminuria, 25% overt nephropathy)
- microalbuminuria is a risk factor for progression to overt nephropathy and cardiovascular disease
- once macroalbuminuria is established, renal function declines, 50% of patients reach ESRD within 7-10 yr
- associated with HTN and diabetic retinopathy (especially type 1 DM) and/or neuropathy (especially type 2 DM)
- indication of possible non-diabetic cause of renal disease in patients with DM
  - rising Cr with little/no proteinuria
  - lack of retinopathy or neuropathy (microvascular complications)
  - persistent hematuria (microscopic or macroscopic)
  - signs or symptoms of systemic disease
  - inappropriate time course; rapidly rising Cr, renal disease in a patient with short duration of DM
  - family history of non-diabetic renal disease (e.g. PCKD, Alport's)

DM is one of the causes of ESRD that does not result in small kidneys at presentation of ESRD; the others are amyloidosis, HIV nephropathy, PCKD, and multiple myeloma

Abnormal Urine ACR Values from 2013 Canadian DM Association CPG
>2.0 mg/mmol in males and females

ACEI can cause hyperkalemia; therefore, be sure to watch serum $K^+$, especially if patient has DM and renal insufficiency

### DIABETIC RENAL COMPLICATIONS

#### 1. Progressive Glomerulosclerosis

- classic diabetic glomerular lesion: Kimmelstiel-Wilson nodular glomerulosclerosis (15-20%)
- more common lesion is diffuse glomerulosclerosis with a uniform increase in mesangial matrix

**Table 14. Stages of Diabetic Progressive Glomerulosclerosis**

| | Stage 1 | Stage 2 | Stage 3 | Stage 4 |
|---|---|---|---|---|
| **Clinical** | ↑ GFR (120-150%) – compensatory hyperfiltration | Detectable microalbuminuria (0-300 mg/24 h)<br>(ACR) 2.0-20 mg/mmol (18-180 mg/d) | Macroalbuminuria (>300 mg/24 h)<br>ACR >20 mg/mmol, (>180 mg/d)<br>Proteinuria (positive urine dipstick)<br>Normal GFR | ↑ proteinuria (>500 mg/24 h)<br>↓ GFR |
| **Pathological** | ± slightly ↑ mesangial matrix | | ↑↑↑ mesangial matrix | Sclerosed glomeruli<br><20% glomerular filtration surface area present |

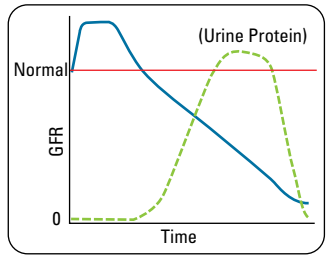



**Figure 17. GFR and urine protein over time in DM**

**Protein Restriction for Diabetic Renal Disease**
*Cochrane DB Syst Rev* 2007;4:CD002181
**Purpose**: To review the effects of dietary protein restriction on the progression of diabetic nephropathy.
**Study Selection**: RCTs and before and after studies of the effects of restricted protein diet on renal function in subjects with DM. 12 studies were reviewed.
**Results**: The risk of end-stage renal disease or death was lower in patients on low-protein diet. In patients with type 1 DM no effect on GFR was noted in the low-protein diet group.

#### 2. Accelerated Atherosclerosis

- common finding
- decreased GFR
- may increase angiotensin II production resulting in increased BP
- increased risk of ATN secondary to contrast media

#### 3. Autonomic Neuropathy

- causes atonic bladder, which leads to functional obstruction and urinary retention
- residual urine promotes infection
- obstructive nephropathy

#### 4. Papillary Necrosis

- type 1 DM susceptible to ischemic necrosis of medullary papillae
- sloughed papillae may obstruct ureter
- can present as renal colic or with obstructive features ± hydronephrosis

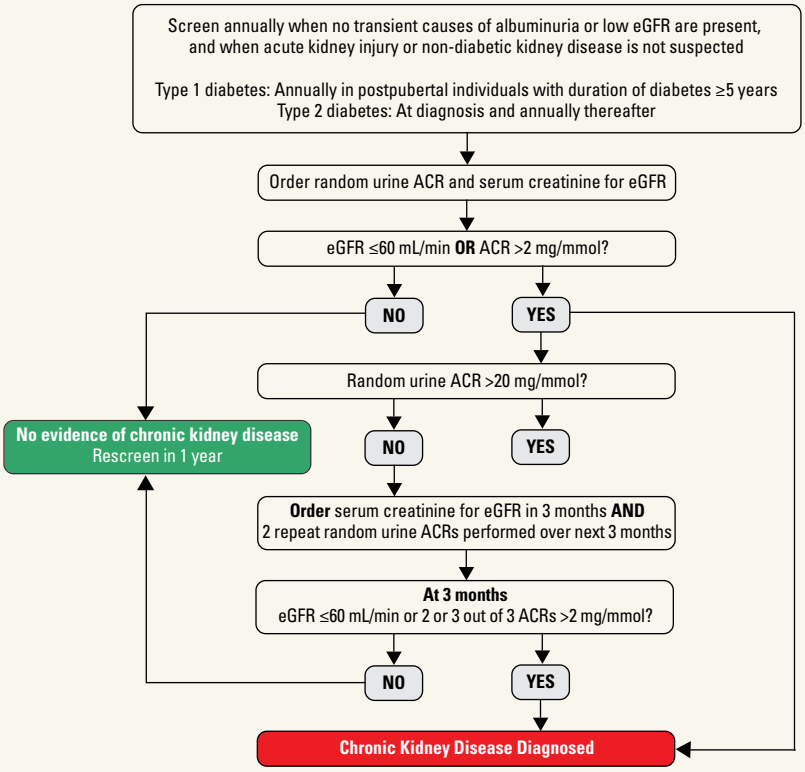



**Figure 18. Clinical practice guidelines on chronic kidney disease in diabetes**
Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes 2013;37(suppl 1):S1-S212

**Renal Outcomes with Telmisartan, Ramipril, or Both in People at High Vascular Risk (ONTARGET Study)**
Lancet 2008;372:547-553
**Study**: Prospective, multicentre, double-blind, RCT.
**Participants**: 25,620 patients with median follow-up of 56 mo.
**Intervention**: Patients received either ramipril (10 mg/d; n=8576), telmisartan (80 mg/d; n=8542), or a combination of both drugs (n=8502).
**Primary Outcome**: Composite of dialysis, doubling of creatinine level, and death.
**Results**: The number of outcome events was similar for telmisartan (n=1147) and ramipril (1150; HR 1.00, 95% CI 0.92-1.09), but was increased with combination therapy (1233; HR 1.09, 1.01-1.18, p=0.037). The need for dialysis or doubling of serum creatinine, was similar with telmisartan (189) and ramipril (174; HR 1.09, 0.89-1.34) and more frequent with combination therapy (212; HR 1.24, 1.01-1.51, p=0.038). Estimated GFR declined least with ramipril compared with telmisartan or combination therapy (p<0.001). The increase in urinary albumin excretion was less with telmisartan (p=0.004) and combination therapy (p=0.001) than with ramipril.
**Conclusion**: Renal outcomes were similar in both telmisartan and ramipril monotherapy. Combination therapy reduced proteinuria to a greater extent than monotherapy, but was associated with poorer renal outcomes.

### Priorities in the Management of Patients with DM

1. vascular protection for all patients with DM
   - ACEI, antiplatelet therapy (as indicated)
   - BP control, glycemic control, lifestyle modification, lipid control
   - Canagliflozin provides renoprotection independent of its glycemic effects
2. optimization of BP in patients who are hypertensive
   - treat according to HTN guidelines
3. renal protection for DM patients with nephropathy (even in absence of HTN)
   - type 1 DM: ACEI or ARB
   - type 2 DM: CrCl >60 mL/min: ACEI or ARB; CrCl <60 mL/min: ARB
   - 2nd line agents: nondihydropyridine calcium channel blockers (diltiazem, verapamil)
   - combination of ACEI and ARB not recommended
4. smoking cessation

- check serum Cr and $K^+$ levels within 1 wk of initiating ACEI or ARB and at time of acute illness
- serum Cr can safely be allowed to rise up to 30% with initiation of ACEI or ARB, usually stabilizes after 2-4 wk, monitor for significant worsening of renal function or hyperkalemia
- if >30% rise in serum Cr or hyperkalemia, discontinue medication and consider 2nd line agent
- consider holding ACEI, ARB, and/or diuretic with acute illness and in women before becoming pregnant
- consider referral to nephrologist if ACR >60 mg/mmol, eGFR <30 mL/min, progressive kidney function loss, unable to achieve BP targets, or unable to stay on ACEI or ARB

## Scleroderma

- see Rheumatology, RH13
- 50% of patients with scleroderma have renal involvement (mild proteinuria, high Cr, HTN)
- renal involvement usually occurs early in the course of illness
- histology: media thickened, "onion skin" hypertrophy of small renal arteries, fibrinoid necrosis of afferent arterioles and glomeruli
- 10-15% of scleroderma patients have a "scleroderma renal crisis" (occurs in first few years of disease): malignant HTN, ARF, microangiopathy, volume overload, visual changes, HTN encephalopathy
- treatment: BP control with ACEI slows progression of renal disease

# Multiple Myeloma

- see Hematology, H49
- malignant proliferation of plasma cells in the bone marrow with the production of immunoglobulins
- patients may present with severe bone disease and renal failure
- light chains are filtered at the glomerulus and appear as Bence-Jones proteins in the urine (monoclonal light chains)
- kidney damage can occur by several mechanisms
  - hypercalcemia
  - light chain cast nephropathy or "myeloma kidney"
  - hyperuricemia
  - infection
  - secondary amyloidosis
  - monoclonal Ig deposition disease
  - diffuse tubular obstruction
- light chain cast nephropathy
  - large tubular casts in urine sediment (light chains + Tamm-Horsfall protein)
  - proteinuria and renal insufficiency can progress rapidly to kidney failure
- monoclonal Ig deposition disease
  - deposits of monoclonal Ig in kidney, liver, heart, and other organs
  - mostly light chains (85-90%)
  - causes nodular glomerulosclerosis (similar to diabetic nephropathy)
- lab features: increased BUN, increased Cr, urine protein immunoelectrophoresis positive for Bence-Jones protein (not detected on urine dipstick)
- poor candidates for kidney transplantation

# Malignancy

- cancer can have many different renal manifestations
- kidney transplantation cannot be performed unless malignancy is cured. Nephrology considerations for malignant presentations include:
  - solid tumours: mild proteinuria or membranous GN
  - lymphoma: minimal change GN (Hodgkin's) or membranous GN (non-Hodgkin's)
  - renal cell carcinoma
  - tumour lysis syndrome: hyperuricemia, diffuse tubular obstruction, hyperkalemia, hyperphosphatemia, hypocalcemia, lactic acidosis
  - chemotherapy (especially cisplatin): ATN or chronic TIN
  - pelvic tumours/mets: postrenal failure secondary to obstruction
  - 2° amyloidosis
  - radiotherapy (radiation nephritis)

# Chronic Kidney Disease

## Definition

- progressive abnormalities of kidney function for >3 mo, with either
  - GFR <60 mL/min/1.73 $m^2$; or
  - markers of kidney damage, including:
  - hematuria, proteinuria, or anatomic abnormalities

## Clinical Features

- volume overload and HTN
- electrolyte and acid-base balance disorders (e.g. metabolic acidosis)
- uremia (e.g. nausea/vomiting, pruritus, encephalopathy)
- anemia
- bone mineral disorders
- sleep disorders common in CKD: insomnia, sleep apnea, restless legs syndrome



**2016 CCS Guidelines for the Management of Dyslipidemia for the Prevention of CVD in the Adult – Chronic Kidney Disease**

Can J Cardiology 2016;32:1263-82

Recommendations:

- Adults ≥50 yr with CKD (GFR <60 mL/min/1.73$m^2$) should receive treatment with a statin or a statin/ezetimibe combination
- Initiation of lipid-lowering therapy is not recommended for adults with dialysis-dependent CKD however, if already receiving it at the time of dialysis initiation, it should be continued
- Statin therapy should be used in adults with kidney transplantation



**Incidence of Etiologies of CKD**

| | |
|---|---|
| DM | 42.9% |
| HTN | 26.4% |
| Glomerulonephritis | 9.9% |
| Other/Unknown | 7.7% |
| Interstitial nephritis/ Pyelonephritis | 4.0% |
| Cystic/Hereditary/Congenital | 3.1% |
| Secondary GN/Vasculitis | 2.4% |



**Management of Complications of CKD**

**NEPHRON**

- **N** – Low-nitrogen diet
- **E** – Electrolytes: monitor $K^+$
- **P** – pH: metabolic acidosis
- **H** – HTN
- **R** – RBCs: manage anemia with erythropoietin
- **O** – Osteodystrophy: give calcium between meals (to increase $Ca^{2+}$) and calcium with meals (to bind and decrease $PO_4^{3-}$)
- **N** – Nephrotoxins: avoid nephrotoxic drugs (ASA, gentamicin) and adjust doses of renally excreted medications

**Table 15. Stages of CKD (KDIGO, 2013)**

| | | | Persistent Albuminuria Categories | | |
|---|---|---|---|---|---|
| | | GFR (mL/min/1.73m²) | A1<br><30 mg/g<br><3 mg/mmol | A2<br>30-300 mg/g<br>3-30 mg/mmol | A3<br>>300 mg/g<br>>30 mg/mmol |
| **GFR Categories (mL/min/1.73m²)** | G1 | ≥90 | 1 if CKD | 1 | 2 |
| | G2 | 60-89 | 1 if CKD | 1 | 2 |
| | G3a | 45-59 | 1 | 2 | 3 |
| | G3b | 30-44 | 2 | 3 | 3 |
| | G4 | 15-29 | 3 | 3 | 4+ |
| | G5 | <15 (kidney failure) | 4+ | 4+ | 4+ |

The numbers in the boxes are a reflection of the risk of progression and are a guide to the frequency of monitoring/year
"D" is added to G5 for patients requiring dialysis
Classification is based on cause, GFR, and amount of albuminuria
Rate of progression and risk of complications are determined by the cause of CKD

# Management of Chronic Kidney Disease

- diet
  - preventing HTN and volume overload
  - low-protein diet
- $Na^+$ restriction
  - preventing electrolyte imbalances
  - target of <2 g/d (5 g/d of salt)
- $K^+$ restriction (40-60 mmol/d)
- $PO_4^{3-}$ restriction (1 g/d)
- avoid extra-dietary $Mg^{2+}$ (e.g. antacids)
  - preventing uremia and potentially delaying decline in GFR
- protein restriction with adequate caloric intake in order to limit endogenous protein catabolism
- medical
  - adjust dosages of renally excreted medications
  - HTN: ACEI (target 140/90 mmHg without DM and 130/80 mmHg with DM), loop diuretics when GFR <25 mL/min
  - dyslipidemia: statins (target LDL <2 mmol/L)
  - calcium and phosphate disorders
- consider vitamin D and calcitriol (1,25-dihydroxy-vitamin D) if hypocalcemic, but hold if hyperphosphatemic (reduces PTH)
- sevelamer (phosphate binder) if both hypercalcemic and hyperphosphatemic
- cinacalcet for hyperparathyroidism (sensitizes parathyroid to $Ca^{2+}$, decreasing PTH)
- metabolic acidosis: sodium bicarbonate
- anemia: erythropoietin injections for Hb <90 g/L (9 g/dL) and target Hb between 90-115g/L (9-10.5 g/dL). IV iron administration often required for iron deficiency
- clotting abnormalities: DDAVP if patient has clinical bleeding or invasive procedures (acts to reverse platelet dysfunction)
- dialysis (see NP38 for indications of dialysis in *Chronic Kidney Disease*)
- renal transplantation for end stage kidney disease

## Prevention of Progression

- as above
- control of HTN, DM (HbA1c <7%), cardiovascular risk factors (e.g. smoking cessation, physical activity, weight loss)
- avoid nephrotoxins such as NSAIDs, COXIBs, IV contrast in patients with eGFR <60 mL/min/1.73 $m^2$
- address reversible causes of AKI



**Renin Angiotensin System Blockade and Cardiovascular Outcomes in Patients with Chronic Kidney Disease and Proteinuria: A Meta-Analysis**
Am Heart J 2008;155:791-805
**Purpose**: To evaluate the role of RAS blockade in improving cardiovascular CV outcomes in patients with CKD.
**Study Selection**: RCT that analyzed CV outcomes in patients with CKD/proteinuria treated with RAS blockade (ACEI/ARB). RAS blockade-based therapy was compared with placebo and control therapy (β-blocker, calcium-channel blockers, and other antihypertensive-based therapy) in the study.
**Results**: Twenty-five trials (n=45,758) were included. Compared to placebo, RAS blockade reduced the risk of heart failure in patients with diabetic nephropathy. In patients with non-diabetic CKD, RAS blockade decreased CV outcome compared to control therapy.
**Conclusions**: RAS blockade reduced CV outcomes in diabetic nephropathy as well as non-diabetic CKD.



**Effects of Lowering LDL Cholesterol with Simvastatin and Ezetimibe in Patients with Chronic Kidney Disease**
Lancet 2011;377:2181-2192
**Purpose**: To assess the efficacy and safety of the combination of simvastatin and ezetimibe in patients with moderate to severe CKD.
**Study**: Randomized, double-blind trial with 9270 patients with CKD with no known history of myocardial infarction or coronary vascularization. Patients were randomized to simvastatin 20 mg plus ezetimibe 10 mg daily versus matching placebo.
**Primary Outcome**: First major atherosclerotic event (non-fatal myocardial infarction or coronary death, non-hemorrhagic stroke, or any arterial revascularization procedure).
**Results**: The simvastatin plus ezetimibe group was associated with an average LDL cholesterol difference of 0.85 mmol/L during a median follow-up of 4.9 yr. There was a 17% proportional reduction in major atherosclerotic events in the simvastatin plus ezetimibe group compared to placebo.
**Conclusions**: Reducing LDL cholesterol with a treatment regimen of simvastatin plus ezetimibe safely reduced the incidence of major atherosclerotic events in patients with moderate to severe CKD.



**Effects of Intensive BP Control in CKD**
J Am Soc Nephrol 2017;28(9):2812-23
**Objective**: To evaluate appropriate target for BP in patients with CKD and HTN.
**Methods**: RCT subgroup analyses of participants in the Systolic Blood Pressure Intervention Trial (SPRINT). Participants were randomly assigned to intensive group (sBP <120 mmHg) or standard group (sBP <140 mmHg).
**Results**: The intensive group had a lower rate of all-cause death (HR 0.72, 95% CI 0.63-1.05) and major CV events (HR 0.81, 95% CI 0.63-1.05). Decreases in eGFR were comparable between treatment groups (HR 0.90, 95% CI 0.44-1.83). Treatment effects did not differ between participants with and without CKD.
**Conclusions**: In patients with CKD and HTN without diabetes, target sBP of 120 mmHg vs. 140 mmHg reduced rates of major CV events and all-cause death.

# Hypertension

- see Family Medicine, FM33
- HTN occurs in about 20% of population
- etiology classified as primary ("essential"; makes up 90% of cases) or secondary
- primary HTN can cause kidney disease (hypertensive nephrosclerosis), which may in turn exacerbate the HTN
- secondary HTN can be caused by renal parenchymal or renal vascular disease

## Hypertensive Nephrosclerosis

**Table 16. Chronic vs. Malignant Nephrosclerosis**

| | Chronic Nephrosclerosis | Malignant Nephrosclerosis |
|---|---|---|
| **Histology** | Slow vascular sclerosis with ischemic changes affecting intralobular and afferent arterioles | Fibrinoid necrosis of arterioles, disruption of vascular endothelium |
| **Clinical Picture** | Black race, underlying CKD, chronic hypertensive disease | Acute elevation in BP (dBP >120 mmHg)<br>HTN encephalopathy |
| **Urinalysis** | Mild proteinuria, normal urine sediment | Proteinuria and hematuria (RBC casts) |
| **Therapy** | Blood pressure control, (target <140/90) with frequent follow-up | Lower dBP to 100-110 mmHg within 6-24 h<br>More aggressive treatment can cause ischemic event<br>Identify and treat underlying cause of HTN |
| **Prognosis** | Can progress to renal failure despite patient adherence | Lower survival if renal insufficiency develops |

## Renovascular Hypertension

- see *Vascular Diseases of the Kidney*, NP28

## Renal Parenchymal Hypertension

- HTN secondary to GN, AIN, diabetic nephropathy, or any other chronic renal disease
- mechanism of HTN not fully understood but may include:
  - excess RAAS activation due to inflammation and fibrosis in multiple small intra-renal vessels
  - production of unknown vasopressors, lack of production of unknown vasodilators, or lack of clearance of endogenous vasopressor
  - ineffective sodium excretion with fluid overload

### Investigations

- as well as investigations for renovascular HTN, additional tests may include
  - 24 h urinary estimations of CrCl and protein excretion
  - imaging (U/S, CT)
  - serology for collagen-vascular disease
  - renal biopsy (very rarely if at all)

### Treatment

- most chronic renal disease is irreversible, but treatment of HTN can slow the progression of renal insufficiency
- control ECF volume: $Na^+$ restriction (2 g/d intake), diuretic, dialysis with end-stage disease
- ACEI or ARB may provide added benefit (monitor $K^+$ and Cr) if there is significant proteinuria (>300 mg/d)

# Cystic Diseases of the Kidney

- characterized by epithelium-lined cavities filled with fluid or semisolid debris within the kidneys
- includes: simple cysts (present in 50% of population >50), medullary cystic kidney, medullary sponge kidney, polycystic kidney disease (autosomal dominant and recessive), and acquired cystic kidney disease (in chronic hemodialysis patients)

## Adult Polycystic Kidney Disease

- autosomal dominant; at least 2 genes: *PKD1* (chr 16p) and *PKD2* (chr 4q)
- *PKD1* (1:400), *PKD2* (1:1000) accounts for about 10% of cases of renal failure
- patients generally heterozygous for mutant *PKD* gene but accumulate a series of second 'somatic hits' precipitating the condition
- *PKD* gene defect leads to abnormal proliferation and apoptosis of tubular epithelial cells leading to cyst growth



Hypercalcemia complicates many cancers and can cause multiple kinds of renal disorders (renal vasoconstriction with reduced GFR, salt-wasting with volume depletion, risk of calcium kidney stones)

- most common extrarenal manifestations: multiple asymptomatic hepatic cysts (33%), mitral valve prolapse (25%), cerebral aneurysm (10%), diverticulosis
- polycystic liver disease rarely causes liver failure, but may form the indication of liver transplant due to space occupying impact which can lead to reduced oral intake and malnutrition
- less common extrarenal manifestations: cysts in pancreas, spleen, thyroid, ovary, seminal vesicles, and aorta

### Signs and Symptoms
- often asymptomatic; discovered incidentally on imaging or by screening those with FHx
- acute abdominal flank pain/dull lumbar back pain
- hematuria (frequently initial sign is microscopic hematuria, otherwise gross hematuria)
- nocturia (urinary concentrating defect)
- extra-renal presentation (e.g. ruptured berry aneurysm, diverticulitis, mitral valve prolapse, aortic regurgitation, tricuspid valve prolapse)
- HTN (increased renin due to focal compression of intrarenal arteries by cysts) (60-75%)
- ± palpable kidneys

**Extra-Renal Manifestations of PCKD**
- Hepatic cysts
- Mitral valve prolapse
- Cerebral aneurysms
- Diverticulosis

### Common Complications
- urinary tract and cyst infections, HTN, chronic renal failure, nephrolithiasis (5-15%), flank and chronic back pain

### Clinical Course
- polycystic changes are always bilateral and can present at any age
- clinical manifestations rare before age 20-25
- kidneys are normal at birth but may enlarge to 10x normal size
- variable progression to renal functional impairment (ESRD in up to 50% by age 60)

**Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease**
NEJM 2017;377:1930-42
**Objectives**: To evaluate the efficacy and safety of the vasopressin V2-receptor antagonist tolvaptan in patients with later-stage autosomal dominant polycystic kidney disease.
**Methods**: Phase III, randomized withdrawal, multicentre, placebo-controlled, double-blind trial.
**Results**: Change in estimated GFR from baseline was -2.34 ml/min/1.732 in the tolvaptan group (95% CI, -2.81 to -1.87) vs. -3.61 ml/min/1.732 in the placebo group (95% CI, -4.08 to -3.14).
**Conclusions**: Tolvaptan resulted in a slower decline than placebo in the estimated GFR over a 1 yr period.

### Investigations
- radiographic diagnosis: best accomplished by renal U/S (enlarged kidneys, multiple cysts throughout renal parenchyma, increased cortical thickness, splaying of renal calyces)
- CT abdo with contrast (for equivocal cases, occasionally reveals more cystic involvement)
- MRI for kidney volume measurement
- gene linkage analysis for PKD1 for asymptomatic carriers
- Cr, BUN, urine R&M (to assess for hematuria)

### Treatment
- goal: to preserve renal function by prevention and treatment of complications
- tolvaptan has been used to slow decline of renal function, however its use has been limited by side effects
- educate patient and family about disease, its manifestations, and inheritance pattern
- genetic counselling: transmission rate 50% from affected parent
- prevention and early treatment of urinary tract and cyst infections (avoid instrumentation of GU tract)
- TMP/SMX, ciprofloxacin: able to penetrate cyst walls, achieve therapeutic levels
- adequate hydration to prevent stone formation
- avoid contact sports due to greater risk of injury to enlarged kidneys
- screen for cerebral aneurysms if family history of aneurysmal hemorrhages
- monitor blood pressure and treat HTN with ACEI
- dialysis or transplant for ESRD (disease does not recur in transplanted kidney)
- may require nephrectomy for symptomatic relief of pain or due to recurrent infections

## Autosomal Recessive Polycystic Kidney Disease

- 1:20,000 incidence
- prenatal diagnosis by enlarged kidneys (due to cystic dilatation of the collecting ducts); if significant in utero can result in Potter sequence
- perinatal death from respiratory failure
- associated with hepatic fibrosis
- patients who survive perinatal period develop CHF, HTN, CKD, portal hypertension
- treated with dialysis, kidney and/or liver transplant

## Medullary Sponge Kidney

- common, autosomal dominant, usually diagnosed in 4th-5th decades
- multiple cystic dilatations in the collecting ducts of the medulla
- renal stones, hematuria, and recurrent UTIs are common features
- an estimated 10% of patients who present with renal stones have medullary sponge kidney
- nephrocalcinosis on abdominal x-ray in 50% patients, often detect asymptomatic patients incidentally
- diagnosis: contrast filled medullary cysts on IVP leading to characteristic radial pattern ("bouquet of flowers"), "Swiss cheese" appearance on histological cross-section
- treat UTIs and stone formation as indicated
- does not result in renal failure

# End Stage Renal Disease

- ESRD represents an irreversible decline in kidney function requiring renal replacement therapy
- no definite definition, but glomerular filtration rate less than 15 mL per minute per 1.73 $m^2$ body surface area, or those requiring dialysis irrespective of glomerular filtration rate

## Presentation of End Stage Renal Disease

### 1. Volume Overload
- due to increase in total body $Na^+$ content
- signs: weight gain, HTN, pulmonary or peripheral edema

### 2. Electrolyte Abnormalities
- high
  - $K^+$ (decreased renal excretion, increased tissue breakdown)
  - $PO_4^{3-}$ (decreased renal excretion, increased tissue breakdown)
  - $Ca^{2+}$ (rare; happens during recovery phase after rhabdomyolysis-induced AKI or in settings where hypercalcemia contributes to renal failure, such as in multiple myeloma or sarcoidosis)
  - uric acid
- low
  - $Na^+$ (failure to excrete excessive water intake)
  - $Ca^{2+}$ (decreased vitamin D activation, hyperphosphatemia, hypoalbuminemia)
  - $HCO_3^-$ (especially with sepsis or severe heart failure)

### 3. Uremic Syndrome
- manifestations result from retention of uremic toxins as well as hormone deficiencies

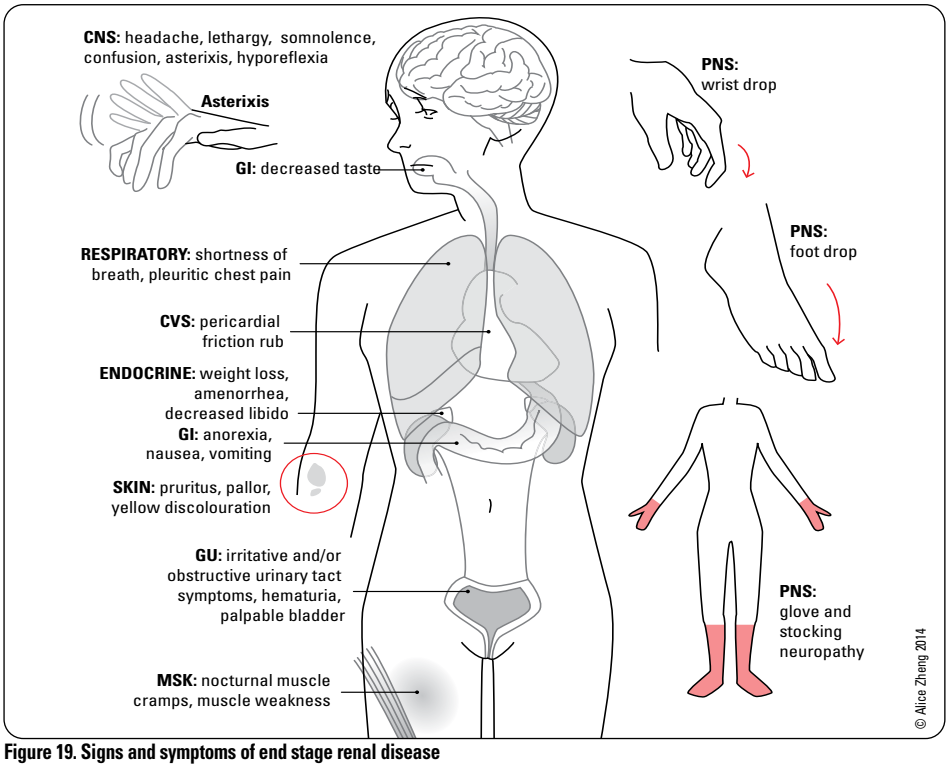



**Figure 19. Signs and symptoms of end stage renal disease**

### Complications
- CNS: decreased LOC, stupor, seizure
- CVS: cardiomyopathy, CHF, arrhythmia, pericarditis, atherosclerosis
- GI: peptic ulcer disease, gastroduodenitis, AVM
- hematologic: anemia, bleeding tendency (platelet dysfunction), infections
- endocrine
  - decreased testosterone, estrogen, progesterone
  - increased FSH, LH
- metabolic
  - renal osteodystrophy: secondary increased PTH due to decreased $Ca^{2+}$, high $PO_4^{3-}$, and low active vitamin D
  - osteitis fibrosa cystica
  - hypertriglyceridemia, accelerated atherogenesis
  - decreased insulin requirements, increased insulin resistance
- dermatologic: pruritus, ecchymosis, hematoma, calciphylaxis (vascular $Ca^{2+}$ deposition)

# Renal Replacement Therapy

## Dialysis

### Indications for Dialysis in Chronic Kidney Disease

**Table 17. Indications for Dialysis**

| Absolute Indications | Relative Indications |
|---|---|
| Volume overload* | Anorexia |
| Hyperkalemia* | Decreased cognitive functioning |
| Severe metabolic acidosis* | Profound fatigue and weakness |
| Neurologic signs or symptoms of uremia (encephalopathy, neuropathy, seizures) | Severe anemia unresponsive to erythropoietin |
| Uremic pericarditis | Persistent severe pruritus |
| Refractory accelerated HTN | Restless leg syndrome |
| Clinically significant bleeding diathesis | |
| Persistent severe N/V | |

*Unresponsive to medications

- decision to start dialysis in ESRD should be symptom driven or when GFR reaches approximately 10 mL/min or lower
  - hemodialysis: blood is filtered across a semipermeable membrane removing accumulated toxic waste products, solutes, excess fluid (ultrafiltration), and restoring buffering agents to the bloodstream
  - available as intermittent (e.g. 3-6x/wk), continuous (CVVHD) or sustained low efficiency (SLED) which are in-hospital treatments
  - can be delivered at home or in-centre, nocturnal
  - vascular access can be achieved through a central line, an artificial AV graft, or an AV fistula
- patients with CKD should be referred for surgery to attempt construction of a primary AV fistula when their eGFR is <20 mL/min, the serum Cr level quoted as >350 μmol/L, or within 1 yr of an anticipated need
- check Kidney Failure Risk Equation, which provides the 2 and 5 year probability of treated kidney failure for a potential patient with CKD stage 3 to 5
- peritoneal dialysis: peritoneum acts as a semipermeable membrane similar to hemodialysis filter
  - advantages: independence, fewer stringent dietary restrictions, better rehabilitation rates
  - available as continuous ambulatory (CAPD; 4-5 exchanges/d) or cyclic (CCPD; machine carries out exchanges overnight)
- refer patients with chronic renal disease to a nephrologist early on to facilitate treatment and plan in advance for renal replacement therapy (RRT)

**Table 18. Peritoneal Dialysis vs. Hemodialysis**

| | Peritoneal Dialysis | Hemodialysis |
|---|---|---|
| **Rate** | Slow | Fast |
| **Location** | Home | Hospital (usually) |
| **Ultrafiltration** | Osmotic pressure via dextrose dialysate | Hydrostatic pressure |
| **Solute Removal** | Concentration gradient and convection | Concentration gradient and convection |
| **Membrane** | Peritoneum | Semi-permeable artificial membrane |
| **Method** | Indwelling catheter in peritoneal cavity | Line from vessel to artificial kidney |
| **Complications** | Infection at catheter site<br>Bacterial peritonitis<br>Metabolic effects of glucose<br>Difficult to achieve adequate clearance in patients with large body mass | Vascular access (clots, collapse)<br>Bacteremia<br>Bleeding due to heparin<br>Hemodynamic stress of extracorporeal circuit<br>Disequilibrium syndrome (headache, cerebral edema, hypotension, nausea, muscle cramps related to solute/water flux over short time) |
| **Preferred When** | Residual renal function<br>Success depends on presence of residual renal function<br>Hemodynamic instability | Comorbidities, no renal function<br>Residual renal function not as important<br>History of abdominal surgery |

## Renal Transplantation

- provides maximum replacement of GFR
- preferred modality of RRT in CKD, not AKI
  - best way to reverse uremic signs and symptoms
  - renal transplantation has been shown to have improved long-term patient survival and greater quality of life over dialysis
- native kidneys usually left *in situ*

**How to Write Dialysis Orders (MUST BE INDIVIDUALIZED)**

- Filter Type (e.g. F80)
- Length (e.g. 4 h 3x/wk or 2 h daily)
- Q Blood Flow (max 500 cc/min)
- Ultrafiltration (e.g. 2 L or to target dry weight)
- $Na^+$ 140 (can be adjusted by starting at 155 and "ramping" down to minimize cramping)
- $K^+$ (based on serum $K^+$)

| Serum $K^+$ | Dialysate |
|---|---|
| 4-6 | 1.5 |
| 3.5-4 | 2.5 |
| <3.5 | 3.5 |

- $Ca^{2+}$ 1.25
- $HCO_3^-$ 40
- Heparin (none, tight [500 U/h] or full [1000 U/h])
- IV fluid to support BP (e.g. NS)

**When to Initiate Dialysis**

CrCl <20 mL/min
- Educate patient regarding dialysis; if not a candidate for peritoneal dialysis, make arrangements for AV fistula

CrCl <15 mL/min
- Weigh risk and benefits for initiating dialysis

CrCl <10 mL/min
- Dialysis should be initiated

**NOTE**

- Cockcroft-Gault equation (or MDRD equation) should be used to measure kidney function
- Monitor for uremic complications
- Significant benefits in quality of life can occur if dialysis started before CrCl <15 mL/min
- It is unclear whether patients who start dialysis early have increased survival
- A preemptive transplant can be considered if patient is stable, in order to avoid dialysis

Source: National Kidney Foundation Kidney Disease Outcomes Quality Initiative

**Commonly Used Immunosuppressive Drugs**

**Calcineurin inhibitors**
- Cyclosporine
- Tacrolimus

**Antiproliferative medications**
- Mycophenolate mofetil
- Azathioprine

**Other agents**
- Sirolimus
- Prednisone

**Anti-lymphocyte antibodies**
- Thymoglobulin
- Basiliximab

**Indications for Dialysis (refractory to medical therapy)**

**AE IOU**
**A**cidosis
**E**lectrolyte imbalance ($K^+$)
**I**ntoxication (AKI)
**O**verload (fluid)
**U**remia (encephalopathy, pericarditis, urea >35-50 mM)

- 2 types: deceased donor, living donor (related or unrelated)
- living donor transplants have been shown to have better short- and long-term outcomes than deceased donor transplants
- kidney transplanted into iliac fossa, transplant renal artery anastomosed to external iliac artery of recipient
- induction immunosuppression with IV thymoglobulin or basiliximab, followed by maintenance oral immunosuppression with an oral immunosuppression cocktail (usually corticosteroids, calcineurin inhibitor, anti-metabolite)
- long-term monitoring of cyclosporin and tacrolimus levels are required
- 1 yr renal allograft survival rates ≥90%

### Complications

- #1 cause of mortality in transplanted patients is cardiovascular disease
- increased risk of infections (bacterial, viral, fungal, opportunistic)
- new-onset DM (often due to prednisone and calcineurin inhibitors, especially tacrolimus)
- graft rejection (cellular or humoral (antibody mediated))
- acute rejection: rise in Cr, fever, hematuria, graft site tenderness, oliguria, although symptoms are very uncommon
- early allograft damage caused by episodes of acute rejection and acute peritransplant injuries
- transplant glomerulopathy from antibody injury
- cyclosporine or tacrolimus nephropathy (see *Small Vessel Disease*, NP29)
- de novo GN (membranous, IgA, MPGN)
- BK virus (polyoma virus) nephropathy can result from over-immunosuppression and lead to graft loss
- leading causes of late allograft loss: interstitial fibrosis/tubular atrophy (IFTA) and death with functioning graft
- depends on immunologic and nonimmunologic factors (HTN, hyperlipidemia, age of donor, quality of graft, new onset DM)
- infections (CMV, PJP and other opportunistic infections usually occur between 1 and 6 mo post-transplant)
- malignancy (skin cancer, Kaposi's sarcoma, non-Hodgkin's lymphoma)



**Survival Benefit with Kidney Transplants from HLA-Incompatible Live Donors**
NEJM 2016;374:940-950
**Purpose**: To assess whether there is a survival advantage to receiving a kidney from HLA-incompatible donors compared to remaining on the waiting list for a possible matched deceased donor kidney.
**Study**: Retrospective, multi-centre analysis
**Population**: 1025 individuals who received HLA-incompatible live donor kidneys compared to two different controls: individuals waiting and possibly receiving a deceased donor kidney (N=5125), or individuals ultimately not receiving a kidney transplant (N=5125).
**Outcome**: Survival, tracked for up to 8 years.
**Results**: Individuals who received HLA incompatible kidneys had increased survival compared to either control group for time points at 1 year, 5 years, and 8 years post-transplant ($p<0.001$). After 8 years non-matched kidney recipients had 76.5% survival compared to 43.9% for individuals who ultimately did not receive a kidney transplant. Survival advantage was significant regardless of how the recipient anti-HLA antibodies were detected.
**Conclusions**: Individuals who received HLA-incompatible kidneys had significantly improved long-term survival compared to individuals who waited for compatible deceased donor kidneys.

# Common Medications

**Table 19. Common Medications in Nephrology**

| Classification | Examples | Site of Action | Mechanism of Action (Secondary Effect) | Indication | Dosing | Adverse Effects |
|---|---|---|---|---|---|---|
| **Loop Diuretics** | furosemide (Lasix®)<br>bumetanide (Bumex®/Buinex®)<br>ethacrynate (Edecrin®)<br>torsemide (Demadex®) | Thick ascending limb of Loop of Henle | ↓ $Na^+/K^+/2Cl^-$ transport ± renal and peripheral vasodilatory effects ($K^+$ loss; ↑ $H^+$ secretion; ↑ $Ca^{2+}$ excretion) | Management of edema secondary to CHF, nephrotic syndrome, cirrhotic ascites;<br>↑ free water clearance (e.g. in SIADH-induced hyponatremia), ↓ BP (less effective due to short action) | furosemide:<br>edema: 20-80 mg IV/IM/PO q6-8h<br>(max 600 mg/d) until desired response<br>HTN: 20-80 mg/d PO OD/bid dosing | Allergy in sulfa-sensitive individuals<br>Electrolyte abnormalities; hypokalemia, hyponatremia, hypocalcemia, hypercalciuria (with stone formation)<br>Volume depletion with metabolic alkalosis<br>Precipitates gouty attacks |
| **Thiazide Diuretics** | hydrochlorothiazide (HCTZ)<br>chlorothiazide (Diuril®)<br>indapamide (Lozol®, Lozide®)<br>metolazone (Zaroxolyn®)<br>chlorthalidone (Hygroton®) | Distal convoluted tubule | Inhibit $Na^+/Cl^-$ transporter ($K^+$ loss; ↑ $H^+$ secretion; ↓ $Ca^{2+}$ excretion) | 1st line for essential HTN<br>Treatment of edema<br>Idiopathic hypercalciuria and stones<br>Diabetes insipidus (nephrogenic) | HCTZ:<br>edema: 25-100 mg PO OD<br>HTN: 12.5-25 mg PO OD<br>(max 50 mg/d)<br>nephrolithiasis/hypercalciuria: 25-100 mg OD | Hypokalemia<br>Increased serum urate levels<br>Precipitates gouty attacks, hypercalcemia<br>Elevated lipids<br>Glucose intolerance |
| **Potassium-Sparing Diuretics** | spironolactone (Aldactone®)<br>triamterene (Dyrenium®)<br>amiloride (Midamor®) | Cortical collecting duct (↓ $Na^+$ reabsorption) | Aldosterone antagonist (spironolactone)<br>Block $Na^+$ channels (triamterene and amiloride) | Reduces $K^+$ loss caused by other diuretics<br>Edema/hypervolemia<br>Severe CHF, ascites (spironolactone), cystic fibrosis (amiloride<br>↓ viscosity of secretions) | spironolactone: 25-200 mg/d OD/bid dosing<br>HTN: 50-200 mg/d OD/bid dosing<br>Hyperaldosteronism: 100-400 mg/d<br>OD/bid dosing<br>amiloride: edema/HTN: 5-10 mg PO OD | Hyperkalemia (caution with ACEI)<br>Triamterene can be nephrotoxic (rare)<br>Nephrolithiasis<br>Gynecomastia (estrogenic effect of spironolactone) |
| **Combination Agents** | Dyazide® (triamterene + HCTZ)<br>Aldactazide®<br>(spironolactone + HCTZ)<br>Moduretic® (amiloride + HCTZ)<br>Vaseretic® (enalapril + HCTZ)<br>Zestoretic® (lisinopril + HCTZ) | | Combination of ACEI and thiazide have a synergistic effect | Combine $K^+$-sparing drug with thiazide to reduce hypokalemia | | |
| **Osmotic Diuretics** | mannitol (Osmitrol®)<br>glycerol<br>urea | Renal tubules (proximal and collecting duct) | Non-reabsorbable solutes increase osmotic pressure of glomerular filtrate – inhibits reabsorption of water and ↑ urinary excretion of toxic materials | To ↓ intracranial or intraocular pressure<br>Mobilization of excess fluid in renal failure or edematous states | mannitol:<br>↓ ICP: 0.25-2 g/kg IV over 30-60 min | Transient volume expansion<br>Electrolyte abnormalities (↓/↑ $Na^+$, ↓/↑ $K^+$) |

**Table 19. Common Medications in Nephrology** (continued)

| Classification | Examples | Site of Action | Mechanism of Action (Secondary Effect) | Indication | Dosing | Adverse Effects |
|---|---|---|---|---|---|---|
| **ACEI** | ramipril (Altace®)<br>enalapril (Vasotec®)<br>lisinopril (Prinivil®)<br>trandolapril (Mavik®)<br>captopril (Capoten®) | Lungs<br>Tissues diffusely | Inhibits angiotension converting enzyme, preventing formation of angiotensin II<br>Prevents angiotensin II vasoconstricting vascular smooth muscle → net vasodilation → ↓ BP<br>Prevents angiotensin II mediated aldosterone release from adrenal cortex and action on proximal renal tubules<br>→ ↑ $Na^+$ and $H_2O$ excretion → ↓ BP<br>Reduces fibrosis and atherogenesis | HTN<br>Cardioprotective effects<br>Renoprotective effects | ramipril: HTN: 2.5-20 mg PO OD/bid dosing<br>renoprotective use; 10 mg PO OD<br>trandolapril: HTN; 1-4 mg PO OD | Cough<br>Asthma<br>Hyperkalemia<br>Angioedema<br>Agranulocytosis (captopril)<br>AKI<br>Teratogenic |
| **ARB** | losartan (Cozaar®)<br>candesartan (Atacand®)<br>irbesartan (Avapro®)<br>valsartan (Diovan®)<br>telmisartan (Micardis®)<br>eprosartan (Teveten®)<br>olmesartan (Olmetec®) | Vascular smooth muscle, adrenal cortex, proximal tubules | Competitive inhibitor at the angiotensin II receptor: prevents angiotensin II vasoconstricting action on vascular smooth muscle → ↓ BP<br>Prevents angiotensin II mediated aldosterone release from adrenal cortex and action on proximal renal tubules → ↑ $Na^+$ and $H_2O$ excretion | HTN<br>Cardioprotective effects<br>Renoprotective effects | HTN:<br>losartan 25-100 mg PO OD<br>candesartan 8-32 mg PO OD<br>irbesartan 150-300 mg PO OD<br>valsartan 80-320 mg PO OD<br>telmisartan 20-80 mg PO OD<br>eprosartan 400-800 mg PO OD<br>olmesartan 20-40 mg PO OD | Hyperkalemia<br>Caution – reduce dose in hepatic impairment<br>AKI<br>Teratogenic |
| **Renin Antagonists** | aliskiren (Rasilez®) | Direct renin antagonist | Inhibits renin production and activity<br>Cardioprotective and renoprotective abilities being evaluated | HTN | aliskiren 150-300 mg PO OD | Hyperkalemia |

# Landmark Nephrology Trials

| Trial | Reference | Results |
|---|---|---|
| 4D | NEJM 2005;353:238-48 | Patients with type 2 DM receiving maintenance hemodialysis were randomized to 20 mg of atorvastatin/d or matching placebo; no difference in composite index of death from cardiac causes, nonfatal myocardial infarction, and stroke |
| AASK | JAMA 2001;285:2719-28 | Ramipril, compared with amlodipine, slows progression of hypertensive renal disease and proteinuria and may benefit patients without proteinuria as well |
| ACCOMPLISH | NEJM 2008;359:2417-20 | Combination treatment with an ACEI and a CCB (benazepril-amlodipine) was more successful than a combination of ACEI and a thiazide diuretic (benzapril-HCTZ) in reducing cardiovascular events in patients with HTN who were at risk for such events |
| ACEI and Diabetic | NEJM 1993;329:1456-62 | Captopril protects against deterioration in renal function in insulin-dependent diabetic nephropathy and is significantly more effective than blood pressure control alone |
| ALERT | Lancet 2003;361:2024-31 | The use of fluvastatin in renal transplant recipients did not significantly decrease the risk of occurrence of a major adverse cardiac event (defined as cardiac death, non-fatal MI, or coronary intervention procedure) compared with placebo; however, there was a significant reduction in cardiac deaths or non-fatal MI |
| ALTITUDE | Early Termination (Unpublished Results;protocol – NDT 2009;24:1663-71) | Combining Aliskiren with ACEI or ARB in high-risk patients with type 2 DM leads to increased incidence of nonfatal stroke, hyperkalemia, and hypotension |
| ASTRAL | NEJM 2009;361:1953-62 | Renal artery revascularization compared to medical therapy does not improve renal function, BP, renal or cardiovascular events, or mortality, and carries significant operative risks |
| AURORA | NEJM 2009;360:1395-407 | Patients receiving maintenance hemodialysis randomized to rosuvastatin 10 mg daily or placebo; rosuvastatin lowered the LDL cholesterol level but had no significant effect on the composite primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke |
| BENEDICT | NEJM 2004;351:1941-51 | Treatment with ACEI trandolapril alone or trandolapril combined with verapamil decreased the incidence of microalbuminuria in patients with type 2 DM and HTN with normoalbuminuria |
| CHOIR | NEJM 2006;355:2085-98 | Patients with CKD were randomly assigned to receive a dose of epoetin alfa targeted to achieve a hemoglobin level of 135 g/L or 113 g/L; the higher target group had an increased risk of death, myocardial infarction, hospitalization for congestive heart failure (without renal replacement therapy), or stroke |
| CORAL | NEJM 2014;370:13-22 | Renal-artery stenting did not confer a significant benefit with respect to the prevention of renal or cardiac events when added to comprehensive, multifactorial medical therapy in people with atherosclerotic renal-artery stenosis and hypertension or chronic kidney disease |
| CREATE | NEJM 2006;355:2071-84 | Patients with CKD (15-35 mL/min) and mild to moderate anemia (110-125 g/L) were randomized to normal (130-150 g/L) or sub-normal (105-115 g/L) hemoglobin levels; early and complete correction of hemoglobin did not reduce the risk of cardiovascular events |
| DETAIL | NEJM 2004;351:1952-61 | The ARB telmisartan and the ACEI enalapril are equally effective in slowing renal function deterioration in type 2 DM with mild to moderate HTN and early nephropathy |

**Landmark Nephrology Trials** (continued)

| Trial | Reference | Results |
|---|---|---|
| ELITE-SYMPHONY | NEJM 2007;357:2562-75 | Daclizumab induction, MMF, steroids, and low-dose tacrolimus effectively maintain stable renal function following renal transplantation, without the negative effects on renal function commonly reported for standard CNI regimens |
| FHN | NEJM 2010;363:2287-300 | Patients were randomized to dialysis 6x/wk (frequent) or 3x/wk (conventional); frequent hemodialysis was associated with improvement in composite outcomes of death, or change in left ventricular mass and death, or change in a physical-health composite score; frequent hemodialysis caused more frequent interventions related to vascular access |
| HEMO | NEJM 2002;347:2010-19 | Use of high dose dialysis or high flux membranes versus standard dose or low flux in thrice-weekly dialysis does not improve survival or outcomes; possible benefit in cardiac-related outcomes with high flux membranes |
| IDEAL | NEJM 2010;363:609-19 | Patients with progressive CKD and GFR between 10 and 15 mL/min randomized to initiate dialysis at GFR of 10-14 mL/min (early) or 5-7 mL/min (late); early initiation of dialysis in patients with stage G5 CKD was not associated with an improvement in survival or clinical outcomes |
| IDNT | NEJM 2001;345:851-60 | Treatment with irbesartan reduced the risk of developing end-stage renal disease and worsening renal function in patients with type 2 DM and diabetic nephropathy |
| IRMA | NEJM 2001;345:870-8 | Irbesartan is renoprotective independently of its blood pressure lowering effect in patients with type 2 DM and microalbuminuria |
| MDRD | Ann Intern Med 1995;123:754-62 | Patients with proteinuria of more than 1 g/d should have a target BP <125/75 mmHg; patients with proteinuria of 0.25 to 1.0 g/d should have a target BP <130/80 mmHg |
| ONTARGET | Lancet 2008;372:547-53 | Telmisartan and ramipril monotherapy reduced proteinuria and rise in Cr in patients with high vascular risk; combination of the two agents led to increased acute renal failure episodes, syncope, and hypotension |
| REIN | Lancet 1999;354:359-64 | In non-diabetic nephropathy, ACEI were renoprotective in patients with non-nephrotic range proteinuria |
| REIN2 | Lancet 2005;365:939-46 | In non-diabetic nephropathy already on ACEI, no further benefit from intensified BP control (sBP/dBP<130/80 mmHg) by adding a CCB versus conventional BP control (dBP<90 mmHg) on ACEI alone |
| RENAAL | NEJM 2001;345:861-9 | Losartan conferred significant renal benefits in patients with type 2 DM and nephropathy and was generally well-tolerated |
| RENAL | NEJM 2009;361:1627-38 | High intensity continuous renal-replacement therapy in AKI does not improve survival or outcomes compared to low intensity treatment, and is associated with higher rates of hypophosphatemia |
| Rituximab in Children with Steroid-Dependent Nephrotic Syndrome | JASN 2015;26 DOI: ASN.2014080799 | Rituximab is non-inferior to steroids in maintaining remission in juvenile steroid dependent nephrotic syndrome |
| ROAD | JASN 2007;18:1889-98 | Uptitration of either ACEI benazepril or ARB losartan to optimal anti-proteinuria doses conferred benefit on renal outcome in patients without DM who had proteinuria and renal insufficiency |
| ROADMAP | NEJM 2011;364:907-17 | The use of the ARB olmesartan was more effective than placebo in delaying the onset of microalbuminuria in patients with type 2 DM, normoalbuminuria, and good blood pressure control; however, a higher rate of fatal cardiovascular events was found amongst patients with preexisting coronary heart disease in the olmesartan group |
| SHARP | Lancet 2011;377:2181-92 | Randomized placebo-controlled trial in patients with CKD and no history of MI or coronary revascularization took simvastatin 20 mg plus ezetimibe 10 mg daily versus matching placebo; simvastatin 20 mg plus ezetimibe 10 mg daily resulted in reduction of LDL cholesterol with associated reduction of major atherosclerotic events in patients with CKD |
| SPRINT | NEJM 2015;373:2103-2116 | A lower blood pressure target of 120/80 mmHg reduced the risk of composite cardiovascular events in a hypertensive patient population |
| TREAT | NEJM 2009;361:2019-32 | Patients with type 2 DM, CKD, and anemia were randomized to darbepoetin targeting a hemoglobin of 13 g/dL or placebo; darbepoetin did not reduce the risk of death, a cardiovascular event, or a renal event, and was associated with an increased risk of stroke |
| Tolvaptan in ADPKD | NEJM 2012;367: 2407-18 | Tolvaptan (vs. placebo) slowed the increase in total kidney volume and decline in kidney function over a 3-year period in patients with ADPKD but was associated with a higher discontinuation rate, due to adverse events |
| SGLT-2 inhibitor use and diabetic | J Am Soc Nephrol 2017; 28:368-375 | Canagliflozin, a sodium-glucose cotransporter 2 inhibitor, slowed the progression of renal disease over 2 years in patients with type 2 diabetes, and may confer renoprotective effects independently of glycemic control |

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# Neurology

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| CN III | CN VI | CN IX | CN XII |

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# Acronyms

| | |
|---|---|
| aPTT | activated partial thromboplastin time |
| ACA | anterior cerebral artery |
| ACEI | angiotensin converting enzyme inhibitor |
| ACh | acetylcholine |
| AD | Alzheimer's disease |
| ADL | activities of daily living |
| AED | antiepileptic drugs |
| AION | acute ischemic optic neuropathy |
| ALS | amyotrophic lateral sclerosis |
| ARI | absolute risk increase |
| AVM | arteriovenous malformation |
| AVPU | alert, verbal, pain, unresponsive |
| CJD | Creutzfeldt-Jakob disease |
| CN | cranial nerve |
| CNS | central nervous system |
| CRPS | complex regional pain syndrome |
| CRVO | central retinal vein occlusion |
| CSF | cerebral spinal fluid |
| CTV | cerebral CT venography |
| CVD | cerebrovascular disease |
| DBS | deep brain stimulation |
| DLB | dementia with Lewy bodies |
| DM | diabetes mellitus |
| EOM | extraocular movement |
| EtOH | ethanol |
| FEF | frontal eye field |
| FTD | frontotemporal dementia |
| GBS | Guillain-Barré syndrome |
| GCA | giant cell arteritis |
| GCS | Glasgow coma scale |
| GPe | Globus pallidus pars externa |
| GPi | Globus pallidus pars interna |
| H/A | headache |
| HD | Huntington's disease |
| HTT | Huntingtin gene |
| IADL | instrumental activities of daily living |
| ICH | intracranial hemorrhage |
| ICP | intracranial pressure |
| IIH | idiopathic intracranial hypertension |
| INO | internuclear ophthalmoplegia |
| INR | international normalized ratio |
| IVIG | intravenous immunoglobulin |
| JCV | John Cunningham virus |
| LEMS | Lambert-Eaton myasthenic syndrome |
| LGB | lateral geniculate body |
| LMN | lower motor neuron |
| LOC | level of consciousness |
| LP | lumbar puncture |
| MAOI | monoamine oxidase inhibitors |
| MCA | middle cerebral artery |
| MG | myasthenia gravis |
| MLF | medial longitudinal fasciculus |
| MMSE | mini mental status examination |
| MoCA | Montreal cognitive assessment |
| MRA | magnetic resonance angiography |
| MRV | magnetic resonance venography |
| MS | multiple sclerosis |
| N/V | nausea and vomiting |
| NCD | neurocognitive dementia |
| NCS | nerve conduction studies |
| NMJ | neuromuscular junction |
| NPH | normal pressure hydrocephalus |
| OA | osteoarthritis |
| PComm | posterior communicating artery |
| PD | Parkinson's disease |
| PHN | Postherpetic neuralgia |
| PICA | posterior inferior cerebral artery |
| PLMS | periodic limb movement in sleep |
| PML | progressive multifocal leukoencephalopathy |
| PPA | primary progressive aphasia |
| PPRF | paramedian pontine reticular formation |
| PSP | progressive supranuclear palsy |
| RAPD | relative afferent pupillary defect |
| REM | rapid eye movement |
| RLS | restless legs syndrome |
| ROM | range of motion |
| rtPA | recombinant tissue plasminogen activator |
| SAH | subarachnoid hemorrhage |
| SDH | subdural hematoma |
| SNc | substantia nigra pars compacta |
| SNr | substantia nigra pars reticulata |
| SNRI | serotonin and norepinephrine reuptake inhibitors |
| SSRIs | selective serotonin receptor inhibitors |
| STN | subthalamic nucleus |
| TBI | traumatic brain injury |
| TCA | tricyclic antidepressant |
| TIA | transient ischemic attack |
| UMN | upper motor neuron |
| VEGF | vascular endothelial growth factor |
| VZV | varicella zoster virus |

# Approach to the Neurological Complaint

## Lesion Localization

- **cortical**
  - contralateral paresis (with differential effect on face and arm vs. leg)
  - UMN injury (hyperreflexia, positive Babinski sign (extensor plantar response), spasticity, no muscle atrophy (early in the disease), pyramidal pattern of weakness (extensor muscle weakness in upper extremities and flexor muscle weakness is lower extremities)
  - cortical sensory loss (hemisensory loss, position sense, two-point discrimination, graphesthesia, stereognosis)
  - dominant hemisphere (aphasia, alexia, agraphia, acalculia, left-right disorientation)
  - non-dominant hemisphere (hemineglect, dysprosody, amusia, constructional apraxia, alien hand syndrome)
  - homonymous hemianopia/quadrantanopia
  - gaze deviation
  - seizure
  - agnosia (visual, auditory)
  - ideomotor and ideational apraxia
- **subcortical**
  - internal capsule: contralateral paresis with equal face, arm, leg involvement without sensory/cortical deficits; contralateral dysmetria/clumsiness and leg paresis
  - basal ganglia: pill-rolling tremor, bradykinesia, festinating gait, hemiballismus, chorea, dystonic posture
  - thalamus: dense sensory loss, contralateral severe pain, cognitive impairment, altered level of awareness
- **brainstem/bulbar (midbrain, pons, medulla)**
  - crossed hemiplegia or sensory loss (i.e. ipsilateral face, contralateral body)
  - ipsilateral ataxia (dysmetria, rapid alternating movements, tandem gait)
  - nystagmus with fast-beating component toward lesion, diplopia, INO (impaired adduction on contralateral gaze), pupillary abnormalities, gaze impairment
  - dysphagia, dysarthria
  - hearing loss, vertigo
  - hiccups
  - ipsilateral Horner's syndrome
- **cerebellum**
  - ipsilateral ataxia (unsteadiness, incoordination)
  - dysmetria, intention tremor
  - dysdiadochokinesia
  - wide-based gait, truncal titubation (staggering, reeling, lurching)
  - scanning speech (explosive speech with noticeable pauses and accentuated syllables)
  - nystagmus, distorted smooth pursuit, oscillopsia
  - pendular reflexes, hypotonia

- **spinal cord**
  - bilateral motor and/or sensory deficits below the lesion without facial involvement
  - sensory level (line below which there is decreased sensation); suspended "cape-like" sensory level (in central cord lesions)
  - LMN signs (flaccid paresis, hypotonia, hyporeflexia, atrophy, fasciculations) at level of lesion; UMN signs below lesion (marked spasticity, pyramidal distribution weakness and extensor plantar response)
  - bowel, bladder, sexual dysfunction
  - saddle anesthesia (i.e. cauda equina)
  - ataxia
- **nerve root**
  - multiple peripheral nerve involvement
  - myotomal/dermatomal deficits
  - back/neck pain radiating to leg/arm
- **peripheral nerve**
  - distal "stocking-glove distribution" sensory loss
  - weakness or sensory loss respecting the distribution of a specific nerve i.e. median nerve, ulnar nerve, radial nerve
  - LMN signs (hypotonia, hyporeflexia or areflexia, fasciculations, atrophy)
- **neuromuscular junction**
  - fluctuating/fatiguable symptoms
  - facial and limb weakness
  - dysphonia, dysarthria
  - ophthalmoparesis (diplopia), ptosis
  - reflexes usually preserved unless severe/advanced or LEMS
- **muscle**
  - usually symmetric proximal weakness (climbing stairs, getting up from chair) without sensory deficits
  - asymmetric myopathic weakness seen in distal myopathies, myositis, glycogen storage diseases, fascioscapulohymeral dystrophy
  - muscle tenderness
  - muscle atrophy



See Online Atlas for Cranial Nerves Exam, Motor Exam, and Sensory Exam Techniques



Battle's sign = mastoid ecchymosis
Raccoon eyes = periorbital ecchymosis

# The Neurological Exam

## General Exam and Mental Status

- **vitals:** pulse (especially rhythm), BP, RR, temperature
- **H&N:** meningismus, head injury/bruises (signs of basal skull fracture: Battle's sign, raccoon eyes, hemotympanum, CSF rhinorrhea/otorrhea), tongue biting
- **CVS:** carotid bruits, heart murmurs
- **mental status:** orientation (person, place, time), LOC (GCS) (see Emergency Medicine, ER4)
  - GCS/15 – Motor/6, Verbal/5 (T= intubated), Eyes/4





If patient has not brought their glasses, have them look through a pinhole for best corrected vision



When testing CN I, avoid noxious smells like ammonia, as this tests CN V

| Points | Eyes | Verbal | Motor |
|---|---|---|---|
| 1 | No eye opening | No verbal response | No motor response |
| 2 | Eye opening to pain | Incomprehensible sounds | Extension to pain |
| 3 | Eye opening to verbal stimulus | Inappropriate words | Flexion to pain |
| 4 | Eye opening spontaneously | Confused | Withdraws from pain |
| 5 | | Oriented | Localizes pain |
| 6 | | | Obeys commands |

- **cognition**
  - Folstein MMSE – /30 (normal: >23, mild impairment 19-23, moderate impairment: 10-18, severe impairment <10 note: dementia is a clinical diagnosis and is not diagnosed by cognitive testing)
  - MoCA – /30 (≥26 is considered normal)
  - frontal lobe testing (test for executive function – i.e. go/no-go test, Luria test, F-word list generation, trails test as well as frontal release signs i.e. grasp, pout-and-snout, rooting, palmomental, glabellar tap)
  - clock drawing



**Screening Neurologic Exam**

- Mental status: orientation (person, place, time), obeys commands, GCS
- Head and neck: examine for lacerations, contusions, deformities, signs of basal skull fracture, flex neck for meningismus if c-spine injury has been ruled out
- Cranial nerve exam: visual fields ± fundoscopy, pupil size and reactivity, extraocular movements, facial strength, hearing to finger rub
- Motor: tone, power in deltoids, triceps, wrist extensors, hand interossei, iliopsoas, hamstrings, ankle dorsiflexors, pronator drift
- Coordination: finger tapping, finger-to-nose, heel-knee-shin
- Gait: tandem gait, heel walking
- Reflexes: plantar, biceps, triceps, patellar, ankle, Babinski
- Sensation: all 4 limbs, including double simultaneous stimulation, vibration sense at great toes

# Cranial Nerve Exam

**Table 1. Cranial Nerve Examination and Associated Deficits**

| Cranial Nerve | Recommended Physical Exams | Signs/Symptoms of Deficit |
|---|---|---|
| **Olfactory (CN I)** | Odour sensation: test each nostril separately | Anosmia (can be associated with loss of taste) |
| **Optic (CN II)** | Visual acuity: test each eye individually; best corrected vision<br>Test visual fields: peripheral visual fields (counting fingers, white pin), central visual field and blind spot (red pin)<br>Assess pupils: direct and consensual pupillary reaction (afferent), swinging flashlight test (for RAPD)<br>Fundoscopy: optic disc edema and pallor, venous pulsations, hemorrhages<br>Colour vision testing (Ishihara plates) | Central vision loss<br>Peripheral vision loss<br>Absence of light reflexes, RAPD<br>Enlarged blind spot<br>Colour desaturation (especially red) |
| **Oculomotor (CN III)** | Assess extraocular movements and nystagmus<br>Test efferent limb of pupillary light response<br>Assess size and shape of pupils; accommodation reflex and saccadic eye movements<br>Test for ptosis (levator palpebrae superioris) | Eyes deviated down and out; ptosis, can demonstrate mydriasis |
| **Trochlear (CN IV)** | Test movement of superior oblique | Vertical diplopia; may tilt head towards unaffected side (Bielschowsky head tilt test); affected eye cannot turn inward and downward |
| **Trigeminal (CN V)** | Test sensation above supraorbital ridge (V1), maxilla or cheeks (V2), mandible (V3)<br>Test corneal reflex (afferent limb)<br>Assess motor function: temporalis, masseter, pterygoids, jaw jerk reflex | Ipsilateral facial dysesthesia and corneal reflex on stimulation ipsilaterally, weakness and wasting of muscles of mastication, deviation of open jaw to ipsilateral side; trigeminal neuralgia |
| **Abducens (CN VI)** | Test movement of lateral rectus | Horizontal diplopia, esotropia (convergent strabismus) and abductor paralysis of ipsilateral eye, leading to difficulty looking laterally with diplopia |
| **Facial (CN VII)** | Test sensorimotor nerve function with muscles of facial expression<br>Test efferent limb of corneal reflex<br>Visceral sensory nerve function to anterior 2/3 of the tongue<br>Visceral motor nerve function to salivary and lacrimal glands<br>Nerve to stapedius (dysfunction results in hyperacusis) | Paralysis of ipsilateral upper and lower facial muscles<br>Loss of lacrimation<br>Decreased salivation, dry mouth<br>Loss of taste to anterior 2/3 of the tongue ipsilaterally<br>LMN lesion = ipsilateral facial weakness<br>UMN lesion = contralateral facial weakness, sparing the eyebrow bilaterally |
| **Vestibulocochlear (CN VIII)** | Vestibular function - nystagmus, caloric reflexes<br>Cochlear function - whisper test, Rinne, Weber | Vertigo, disequilibrium, and nystagmus<br>Sensorineural hearing loss |
| **Glossopharyngeal (CN IX)** | Assess vocal cord function and gag reflex<br>Assess taste to posterior third of the tongue (bitter and sour taste) | Loss of taste in posterior third of ipsilateral tongue<br>Loss of gag reflex and dysphasia<br>Unilateral lesion is rare |
| **Vagus (CN X)** | Assess vocal cord function: guttural ("ga") and palatal ("ka") articulation<br>Assess gag reflex<br>Observe uvula deviation and palatal elevation<br>Assess swallowing | Loss of gag reflex, dysphagia, hoarse voice<br>Paralysis of soft palate (failed elevation)<br>Deviation of uvula to contralateral side of lesion; anesthesia of pharynx and larynx ipsilaterally |
| **Accessory (CN XI)** | Assess strength of trapezius (shoulder shrug) and sternocleidomastoid muscles (head turn) | Ipsilateral shoulder weakness and turning head to opposite side |
| **Hypoglossal (CN XII)** | Inspect tongue for signs of lateral deviation, atrophy, fasciculations, asymmetry of movement and strength | Wasting of ipsilateral tongue muscles and deviation to ipsilateral side on protrusion |

**CN Innervation of EOM**
LR: CN VI, SO: CN IV, Other: CN III

Contraction of the left sternocleidomastoid turns the head right

**Calorics: Brainstem Test**
Describe nystagmus by direction of fast component

**COWS**
**C**old
**O**pposite
**W**arm
**S**ame

**Upper Motor Neuron Tests**
**Babinski Reflex**: 'Up-going' big toe ± fanning of toes indicates an UMN lesion
**Hoffmann's Reflex**: Flexion of IP joint of the thumb when tapping/flicking/flexing the nail of the index or ring finger may indicate an UMN lesion if asymmetrical
**Pronator Drift**: Unable to maintain full arm extension and supination; side of forearm pronation reflects contralateral pyramidal tract lesion; closing eyes accentuates effect

**Pyramidal Pattern of Muscle Weakness (i.e. UMN)**
**Weaker arm extensors**: shoulder abduction, elbow extension, wrist extension, finger extension, finger abduction
**Weaker leg flexors**: hip flexion, knee flexion, ankle dorsiflexion

**Primitive Reflexes**
Grasp, palmomental, root, glabellar tap, snout

# Motor Exam

- bulk: atrophy, asymmetry
- tone: hypotonia (flaccid), hypertonia (spasticity, rigidity, paratonia), cogwheeling
- power: pronator drift, asymmetric forearm rolling test (satellite sign)
- reflexes: deep tendon reflexes, abdominal reflexes, primitive reflexes, Babinski sign, Hoffmann sign, clonus
- abnormal movements: tremors, chorea, dystonia, dyskinesia, hemiballism, myoclonus, athetosis, tics, fasciculations, myokymia
- abnormal posturing: decorticate (upper extremity flexion, lower extremity extension), decerebrate (extremity extension)

**Table 2. Localization of Motor Deficits**

| | LMN | UMN | Extrapyramidal |
|---|---|---|---|
| **Muscle Tone** | Flaccid | Spastic | Rigid |
| **Involuntary Movements** | Fasciculations | None | None |
| **Reflexes** | Decreased | Increased | Normal |
| **Plantar Reflex** | Down-going (flexor) | Up-going (extensor, i.e. Babinski sign) | Down-going (flexor) |
| **Pattern of Muscle Weakness** | Proximal, distal, or focal | Pyramidal pattern: look for hemiparetic gait (flexed arm, extended legs)<br>Upper extremities: extensors weaker than flexors<br>Lower extremities: flexors weaker than extensors | None |

**Table 3. Overview of Neuromuscular Diseases**

| | Motor Neuron Disease (i.e. ALS) | Peripheral Neuropathy | Neuromuscular Junction | Myopathy |
|---|---|---|---|---|
| **SIGNS AND SYMPTOMS** | | | | |
| **Weakness** | Segmental and asymmetrical, distal to proximal | Distal (except GBS) but may be asymmetrical | Proximal and fatigable (e.g. MG), or weak then recovers (e.g. LEMS) | Proximal (with some exceptions) |
| **Fasciculations** | Yes | Yes | No | No |
| **Reflexes** | Combined hyperreflexia and decreased/absent reflexes | Decreased/absent | Normal | Normal (until late) |
| **Sensory** | No | Yes | No | No |
| **Autonomic*** | No | Yes | No | No |
| **TESTS** | | | | |
| **EMG** | Denervation and reinnervation | Signs of demyelination ± axonal loss | Decremental response, jitter on single fibre EMG | Small, short motor potentials |
| **NCS** | Normal | Abnormal | Normal | Normal |
| **Muscle Enzyme** | Normal | Normal | Normal | Increased (early/mid stage)<br>Normal/decreased (late stage) |

*e.g. orthostatic hypotension, anhidrosis, visual blurring, urinary hesitancy or incontinence, constipation, erectile dysfunction

**Table 4. Approach to Strength Testing of Radiculopathies vs. Peripheral Neuropathies**

How to use this table: For each nerve root, learn two (or more) peripheral nerves (and their associated muscles/movements). In radiculopathies, all associated peripheral nerves (and their movements) will be impaired, whereas in peripheral neuropathies, only one of the nerves (and its movement) will be impaired, sparing the other nerve. Particularly useful peripheral nerve "pairs" are bolded for emphasis.

| Root | Peripheral Nerve | Movement | Muscle |
|---|---|---|---|
| **C5** | Axillary | Shoulder abduction | Deltoid |
| **C6** | Musculocutaneous (C5/6)<br>Radial (C6) | Elbow flexion<br>Wrist extension | Biceps<br>Brachioradialis<br>Extensor carpi radialis longus |
| **C7** | Radial<br>Posterior interosseus | Elbow extension<br>Finger extension | Triceps<br>Extensor digitorum communis |
| **C8, T1** | **Median** | Thumb flexion<br>Thumb abduction<br>Opposition | Flexor pollicis brevis (look for thenar wasting)<br>Abductor pollicis brevis (look for thenar wasting)<br>Opponens pollicis (look for thenar wasting) |
| | **Ulnar** | Finger abduction | First dorsal interosseus (look for wasting in first dorsal webbed space) |
| **L2, 3, 4** | **Femoral**<br>**Obturator** | Hip flexion<br>Hip adduction | Iliopsoas<br>Adductor muscles |
| **L3, 4** | Femoral (L3/4)<br>Deep peroneal (L4/5) | Knee extension<br>Dorsiflexion | Quadriceps<br>Tibialis anterior |
| **L5** | Sciatic (L5, S1)<br>**Tibial**<br>**Superficial peroneal**<br>Deep peroneal | Hip extension<br>Ankle inversion<br>Ankle eversion<br>Big toe extension | Gluteus maximus<br>Tibialis posterior<br>Peroneal muscles<br>Extensor hallucis longus |
| **S1** | Sciatic<br>Tibial | Knee flexion<br>Plantar flexion | Hamstring muscles<br>Gastrocnemius and soleus |

# Sensory Exam

- **primary sensation**
  - spinothalamic tract: crude touch, pain, temperature
  - dorsal column-medial lemniscus pathway: fine touch, vibration, proprioception
- **cortical sensation**
  - graphesthesia, stereognosis, extinction (tactile, visual, auditory), 2-point discrimination

Note: If primary sensation is not intact, this precludes the testing of cortical sensation. Deficits in cortical sensation are typically a sign of contralateral parietal lobe lesions



**MRC Muscle Strength Scale**
5 Full power
4 Submaximal power against resistance (ranging 4+, 4, 4-)
3 Full ROM against gravity without resistance
2 Full ROM with gravity removed
1 Muscle flicker
0 No muscle contraction



**Deep Tendon Reflexes**

| Root | Muscle Tendon |
|---|---|
| C5/6 | Biceps |
| C6 | Brachioradialis |
| C7 | Triceps |
| C8 | Finger flexors |
| L2/3 | Hip adductors |
| L3/4 | Knee extensors |
| S1/2 | Plantar flexion |



**Deep Tendon Reflex Scoring**
0 Absent
1+ Depressed – elicited with reinforcement only
2+ Normal
3+ Increased
4+ Clonus (≥4 beats)



**Interpreting a Slow or Uncoordinated Rapid Alternating Movement (RAM)**
- Slow RAMs without fatiguing is suggestive of weakness (especially if it is asymmetric)
- Slow RAMs with fatiguing (i.e. decreasing amplitude over time) is suggestive of Parkinsonism
- Uncoordinated RAM is suggestive of cerebellar disorder (i.e. ataxia and irregularly irregular rhythm) or ideomotor apraxia



**Common Cerebellar Findings**
Frontal executive dysfunction/disinhibition, scanning speech, nystagmus, hypermetric saccades, hypotonia, pendular reflexes, intention tremor, ataxic finger-nose/heel-shin/tandem, wide based stance and gait, positive rebound
Midline cerebellar diseases: truncal ataxia
Lateral cerebellar hemisphere diseases: limb ataxia



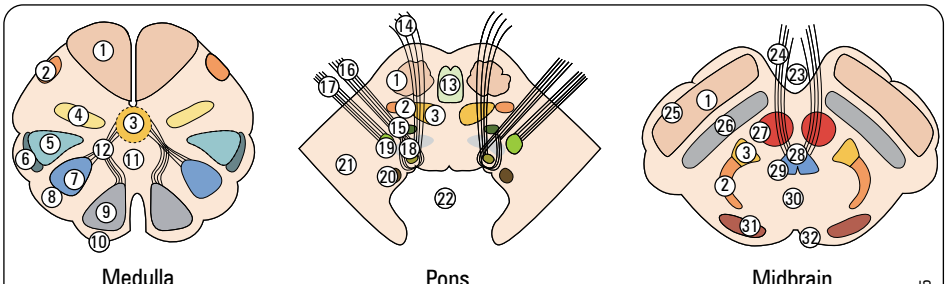
**Romberg Test**
Stable with eyes open and closed = normal
Stable with eyes open, falls with eyes closed = positive Romberg, suggesting loss of joint position sense

# Coordination Exam and Gait

- coordination exam
  - finger-to-nose, heel-to-shin, knee taps, rapid alternating movements
- stance and gait
  - Romberg test
  - pull test or push and release test for postural instability
  - gait: antalgic, hemiplegic, ataxic, apraxic, Parkinsonian gait, steppage gait, broad-based
  - tandem gait (heel-to-toe test)

See Functional Neuroanatomy software

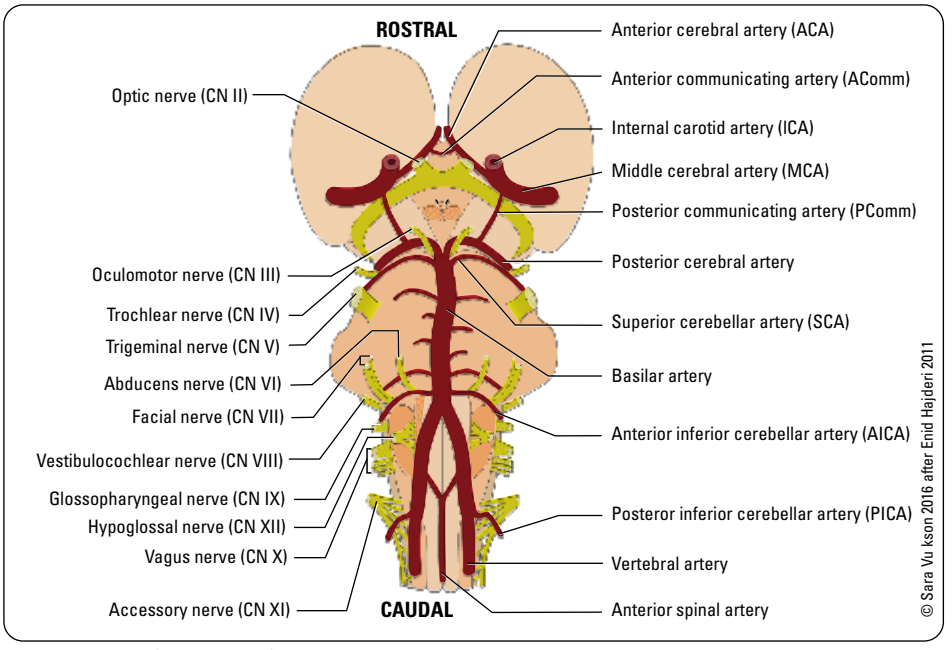
# Basic Anatomy Review




| | | | | | |
|---|---|---|---|---|---|
| 1 | Corticospinal tract | 13 | Pontine nucleus | 23 | Interpeduncular fossa |
| 2 | Spinothalamic tract | 14 | Abducens (VI) nerve fibres | 24 | Oculomotor (III) nerve fibres |
| 3 | Medial lemniscus | 15 | Nucleus of facial (VII) nerve (motor) | 25 | Cerebral peduncle |
| 4 | Reticular formation | 16 | Facial (VII) nerve fibres | 26 | Substantia nigra |
| 5 | Nucleus of spinal tract of trigeminal (V) nerve (descending) | 17 | Trigeminal (V) nerve fibres | 27 | Red nucleus |
| 6 | Spinal tract of trigeminal (V) nerve | 18 | Nucleus of abducens (VI) nerve | 28 | Edinger-Westphal nuclei |
| 7 | Nucleus cuneatus | 19 | Nucleus of spinal tract of trigeminal (V) nerve | 29 | Oculomotor (III) nucleus complex (motor) |
| 8 | Fasciculus cuneatus | 20 | Lateral vestibular nucleus | 30 | Cerebral aqueduct |
| 9 | Nucleus gracilis | 21 | Middle cerebellar peduncle | 31 | Pretectal area |
| 10 | Fasciculus gracilis | 22 | Fourth ventricle | 32 | Superior colliculus |
| 11 | Central canal | | | | |
| 12 | Arcuate fibres | | | | |

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**Figure 1. Brainstem (axial view)**




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**Figure 2. Brainstem (posterior view)**

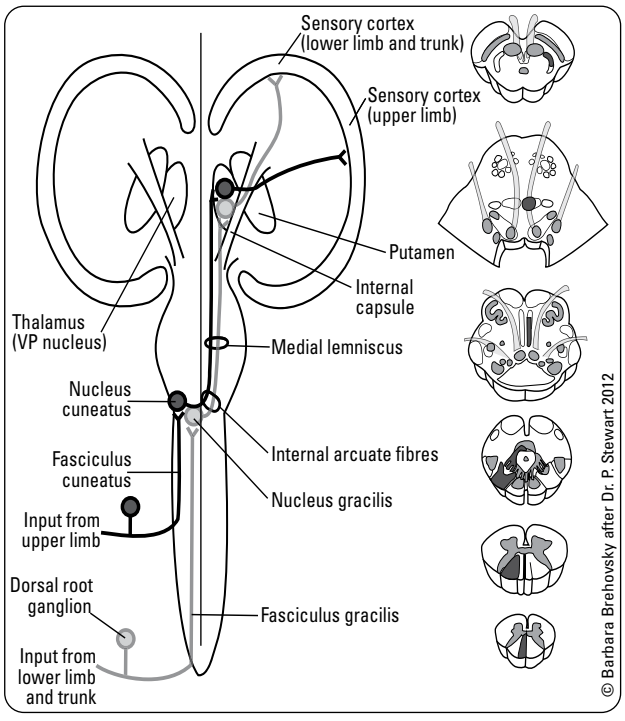



**Figure 3. Discriminative touch pathway (dorsal column) from body**

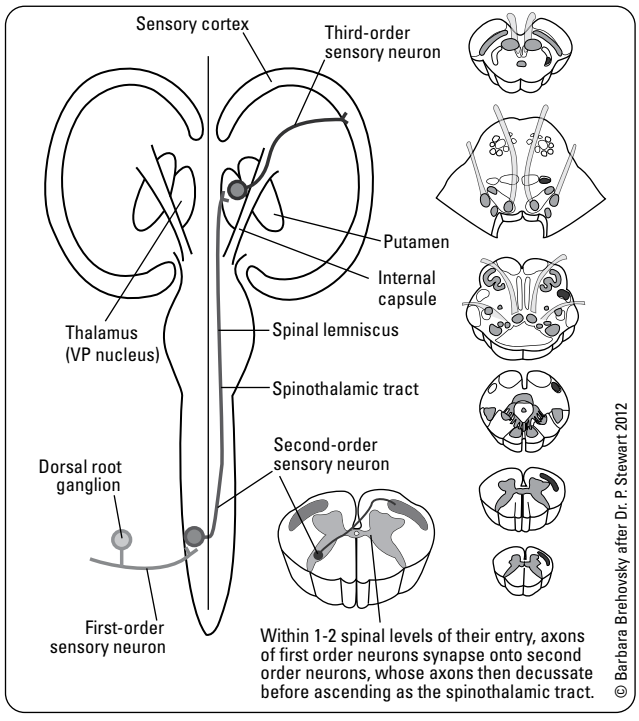



**Figure 4. Spinothalamic tract from body**

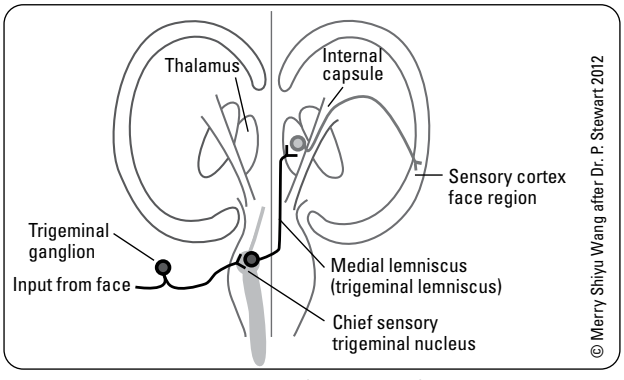



**Figure 5. Discriminative touch pathway (dorsal column) from face**

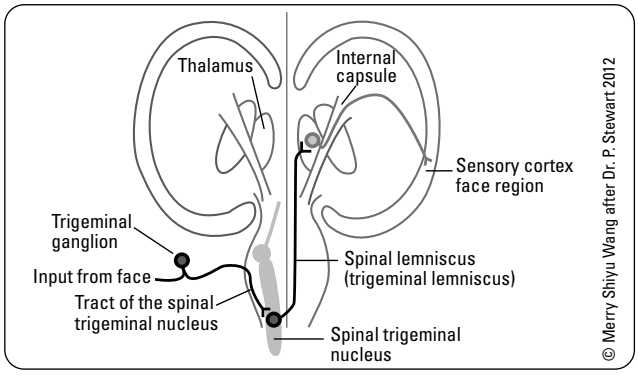



**Figure 6. Spinothalamic tract pathway from face**

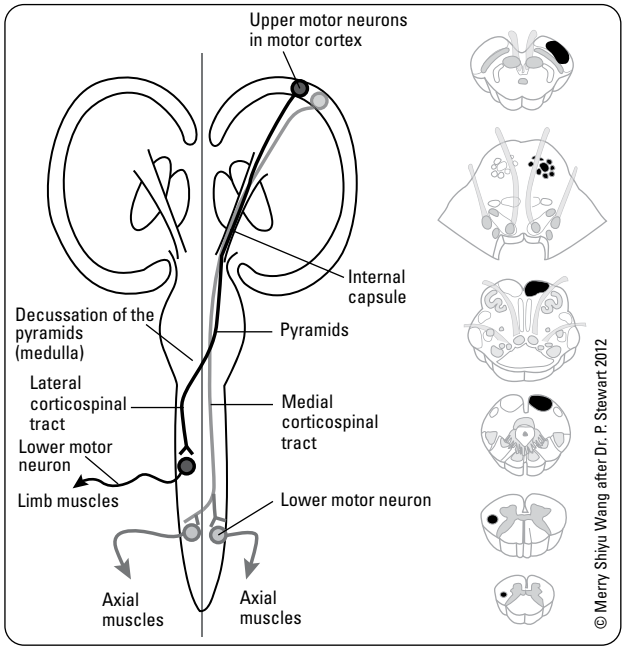



**Figure 7. Corticospinal motor pathway**

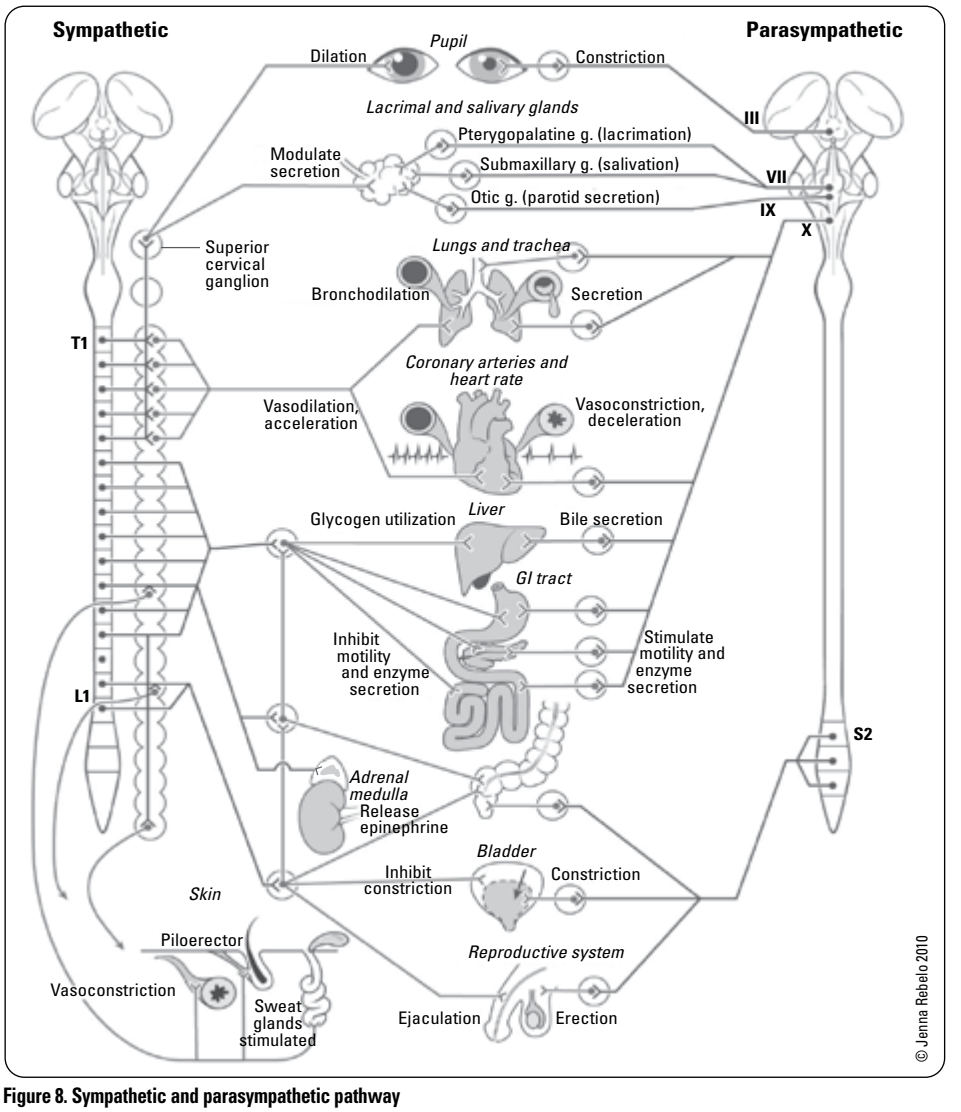



**Figure 8. Sympathetic and parasympathetic pathway**

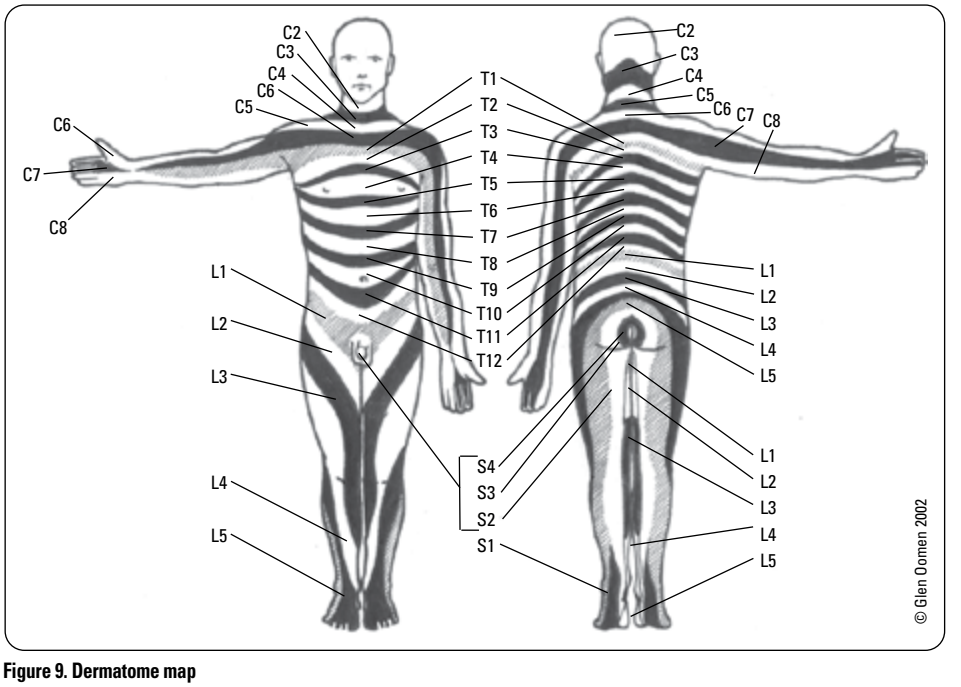



**Figure 9. Dermatome map**

**Myotomes**
C5 – Shoulder abduction/elbow flexion
C6 – Wrist extensors
C7 – Elbow extension
C8 – Finger flexion
T1 – Finger abduction
T2-9 – Intercostal (abdominal reflexes)
T9-10 – Upper abdominals
T11-12 – Lower abdominals
L2 – Hip flexion
L3 – Hip adduction
L4 – Knee extension and ankle dorsiflexion
L5 – Ankle dorsiflexion and big toe extension
S1 – Plantarflexion

# Lumbar Puncture

### Indications
- diagnostic: CNS infection (meningitis, encephalitis), inflammatory disorder (MS, Guillain-Barré, vasculitis), subarachnoid hemorrhage (if CT negative), CNS neoplasm (neoplastic meningitis)
- therapeutic: to administer anesthesia, chemotherapy, contrast media
  - to decrease ICP (pseudotumour cerebri, NPH)

### Contraindications
- mass lesion causing increased ICP, could lead to cerebral herniation; CT first if suspect mass lesion
- infection over LP site/suspected epidural abscess
- low platelets (<50,000) or treatment with anticoagulation (high INR or aPTT)
- uncooperative patient
- acute confirmed/suspected spinal trauma or congenital spinal abnormalities



The needle for a LP is inserted into one of L3-4, L4-5, or L5-S1 interspaces

### Complications
- tonsillar herniation (rare)
- SDH (rare)
- transient 6th nerve palsy (rare)
- post-LP headache (5-40%): worse when upright, better supine; generally onset within 24 h
  - prevention: smaller gauge (i.e. 22) needle, reinsert stylet prior to needle removal, blunt-ended needle
  - symptomatic treatment: caffeine and sodium benzoate injection
  - corrective treatment: blood patch (autologous)
- spinal epidural hematoma
- infection



Do not delay antibiotics while waiting for a LP if infection is suspected

### LP Tubes
- **tube #1:** cell count and differential: RBCs, WBCs, and differential
  - xanthochromia (yellow bilirubin pigmentation implies recent bleed into CSF, diagnostic of SAH)
- **tube #2:** chemistry: glucose (compare to serum glucose) and protein
- **tube #3:** microbiology: Gram stain and C&S
  - specific tests depending on clinical situation/suspicion
    - viral: PCR for herpes simplex virus (HSV) and other viruses
    - bacterial: polysaccharide antigens of *H. influenzae, N. meningitidis, S. pneumoniae*
    - fungal: cryptococcal antigen, culture
    - TB: acid-fast stain, TB culture, TB PCR
- **tube #4:** cytology: for evidence of malignant cells, if clinical suspicion is low for neoplasm, consider sending tube #4 for cell count



RBCs in tube #1>>#5 → traumatic tap
RBCs in tube #1=#5 → SAH

**Table 5. Lumbar Puncture Interpretation (Normal vs. Various Infectious Causes)**

| Condition | Colour | Protein | Glucose | White Blood Cells |
|---|---|---|---|---|
| **NORMAL** | Clear | <0.45 g/L | 60% of serum glucose or >3.0 mmol/L | 0-5 x $10^6$/L |
| **Viral Infection** | Clear or opalescent | Normal or slightly increased<0.45-1 g/L | Normal | <1000 x $10^6$/L Lymphocytes mostly, some PMNs |
| **Bacterial Infection** | Opalescent yellow, may clot | >1 g/L | Decreased (<25% serum glucose or <2.0 mmol/L) | >1000 x $10^6$/L PMNs |
| **Granulomatous Infection (tuberculosis, fungal)** | Clear or opalescent | Increased but usually <5 g/L | Decreased (usually <2.0-4.0 mmol/L) | <1000 x $10^6$/L Lymphocytes |

# Approach to Common Presentations



## Weakness

### Approach
- **mode of onset:** abrupt (vascular, toxic, metabolic), subacute (neoplastic, infective, inflammatory), insidious (hereditary, degenerative, endocrine, neoplastic)
- **course:** worse at onset (vascular), progressive (neoplastic, degenerative, infective), episodic (vascular, inflammatory), activity dependent (NMJ, muscular)
- **pattern:** objective vs. subjective, generalized vs. localized, asymmetric vs. symmetric, proximal vs. distal, UMN vs. LMN, peripheral vs. myotomal
- **associated symptoms:** sensory, cortical, autonomic, spinal (i.e. bowel/bladder dysfunction), signs/symptoms specific to various etiologies
- **history:** family history, developmental history, medications, risk factors, recent/preceding exposures
- **investigations for LMN:** NCS/EMG
- **investigations for UMN:** imaging (brain and/or spinal cord)

### Differential Diagnosis

- objective muscle weakness; also, differentiate between true muscle weakness vs. fatigue
  - generalized
    - myopathy (proximal > distal weakness)
      - endocrine: hypothyroidism, hyperthyroidism, Cushing's syndrome
      - rheumatologic: polymyositis, vasculitis
      - infectious: HIV, influenza
      - other: collagen vascular disorders, steroids, statins, alcohol, electrolyte disorders
    - NMJ (MG, botulism, LEMS, organophosphate poisoning)
    - cachexia
  - localized
    - UMN (vasculitis, abscess, brain tumour, vitamin B12 deficiency, MS, stroke)
    - radicular pain (i.e. nerve root)
    - anterior horn cell (spinal muscular atrophy, ALS, polio, paraneoplastic)
    - peripheral neuropathy (peroneal muscle atrophy, GBS, leprosy, amyloid, myeloma, DM, lead toxicity)
- no objective muscle weakness
  - chronic illness (cardiac, pulmonary, anemia, infection, malignancy)
  - depression, deconditioning

## Numbness/Altered Sensation

### Approach

- positive sensory symptoms: paresthesia/dysesthesia = tingling, pins and needles, prickling, burning, stabbing
- negative sensory symptoms: hypoesthesia/anesthesia = numbness, reduction/absence of feeling
- determine distribution of sensory loss:
  - nerve root vs. peripheral nerve
  - symmetric stocking-glove pattern (indicative of distal symmetric polyneuropathy)
  - dissociated sensory loss: dorsal column (fine touch, proprioception, vibration) vs. spinothalamic tract (pain and temperature)
- investigations: NCS, blood glucose, vitamin B12 levels, imaging based on associated findings

### Differential Diagnosis

- cerebral: stroke, demyelination, tumour
  - symptoms: hemiplegia, aphasia, apraxia
- brainstem: stroke, demyelination, tumour
  - symptoms: diplopia, vertigo, dysarthria, dysphagia, crossed sensory and/or motor findings
- spinal cord/radiculopathy: cord infarction, tumour, MS, syringomyelia, vitamin B12 deficiency, disc lesion
  - symptoms: back/neck pain, weakness (paraparesis or Brown-Séquard pattern)
- neuropathy: focal compressive neuropathy (based on location and distribution), DM, uremia, vasculitis, vitamin B12 deficiency, HIV, Lyme disease, alcohol, paraneoplastic, amyloid

## Gait Disturbance

### Approach

**1. Characterization of the gait disturbance**
- posture, stride length, width between feet, height of step, stability of pelvis, symmetry, arm swing, difficulty turning, tremor, elaborate/inconsistent movements, standing from sitting

**2. Identification of accompanying neurologic signs**
- full neurological exam required (diagnosis often can be made by physical exam alone)

**3. Identify red flags**
- sudden onset, cerebellar ataxia, paresis (hemi-, para- or quadri-), bowel/bladder incontinence

**4. Workup**
- based on etiology – requires blood work, neuroimaging, and urgent neurologist referral



**Central Motor Systems**

**3 components to the control of gait:**
- Pyramidal: main outflow from cortex to spinal cord
- Extrapyramidal: basal ganglia inhibits excess movements
- Cerebellum: affects coordination of gait

**Table 6. Types of Gait Disturbance**

| Location | Description | Disorder |
|---|---|---|
| **Visual Loss** | Broad based gait with tentative steps | Cataract surgery without lens replacement |
| **Proprioceptive Loss** | Sensory ataxia: wide-based with high stepping posture and positive Romberg | Demyelinating neuropathies, paraneoplastic syndrome, tabes dorsalis, MS, compressive myelopathy, B12 deficiency |
| **Peripheral Vestibular Lesion**<br>1. Acute<br>2. Bilateral | 1. Vestibular ataxia<br>2. Disequilibrium | 1. Tumour, trauma, infectious, Ménière's disease<br>2. Ototoxic drugs |
| **Peripheral Nerve Disorder**<br>1. Foot drop<br>2. Lumbosacral radiculopathy | Steppage gait | Acquired/hereditary peripheral neuropathy, compressive peroneal neuropathy, L4-5 radiculopathy |
| **Myopathies** | Waddling gait: broad based, short stepped gait with pronounced lumbar lordosis, rotation of pelvis | Progressive muscular dystrophy |
| **Pyramidal/Corticospinal Tract Lesion**<br>1. Unilateral<br>2. Bilateral | Spastic gait: spastic foot drop, circumduction, scissoring of legs or toe walking with bilateral circumduction | Unilateral: stroke (ischemic/hemorrhagic)<br>Bilateral: cervical spondylosis, cerebral palsy, spinal cord tumour, combined spinal cord degeneration, MS, motor neuron disease |
| **Basal Ganglia** | 1. Parkinsonian gait: small paces, stooped posture, reduced armswing<br>2. Choreic/hemiballistic/dystonic gait | Infarct, Huntington's, Sydenham's chorea, Wilson's disease, SLE, neuroleptic medications, polycythemia vera, genetic dystonia |
| **Cerebellar Disorder** | Cerebellar ataxic gait: wide-based without high stepping; veers to side of lesion<br>Alcoholic gait | Primary and secondary neoplasm, toxins (alcohol), vitamin E deficiency, hypothyroid, hypoxia, hypoglycemia, paraneoplastic syndrome |

# Cranial Nerve Deficits

## CN I: Olfactory Nerve

### Clinical Features
- anosmia associated with a loss of taste

### Differential Diagnosis
- nasal: physical obstruction
  - heavy smoking, chronic rhinitis, sinusitis, neoplasms, septal deformity, choanal atresia, vestibular stenosis, foreign body
- olfactory neuroepithelial: destruction of receptors or their axon filaments
  - influenza, herpes simplex, interferon treatment of hepatitis C virus, atrophic rhinitis (leprosy)
- central: lesion of olfactory pathway
  - Kallmann syndrome, albinism, head injury, cranial surgery, SAH, chronic meningeal inflammation, meningioma, aneurysm, PD, MS

If anosmia is not associated with loss of taste, consider malingering

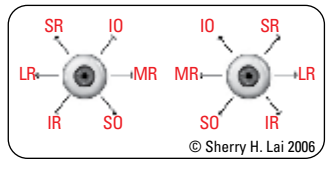



**Figure 10. Diagnostic positions of gaze to isolate the primary action of each muscle**

Kallmann syndrome is a congenital disorder of anosmia and hypogonadotropic hypogonadism

## CN II: Optic Nerve

- see *Neuro-Ophthalmology*, N14

## CN III: Oculomotor Nerve

### Clinical Features
- ptosis, resting eye position is "down and out" (depressed and abducted), pupil dilated (mydriasis)
- vertical and horizontal diplopia; paralysis of adduction, elevation, and depression

### Differential Diagnosis
- **PComm aneurysm:** early mydriasis, then CN III palsy
- **cavernous sinus** (internal carotid aneurysm, meningioma, sinus thrombosis): associated with deficits in other CNs near the cavernous sinus
- **midbrain lesion:** complete unilateral CN III palsy with bilateral weakness of the superior rectus and ptosis with contralateral pyramidal signs ± mydriasis
- **orbital lesion:** associated with optic neuropathy, chemosis, proptosis
- **other:** inflammatory, infection, neoplasia, uncal herniation, trauma

Pupillary constrictor fibres run along outside of nerve, whereas vasculature is contained within nerve
For CN III palsy with a reactive pupil, always think ischemic cause ("pupil sparing")
For CN III palsy with mydriasis, think compressive lesion

Lesions involving the cavernous sinus can lead to cranial nerve palsies of III, IV, VI, V1, and V2 as well as orbital pain and proptosis

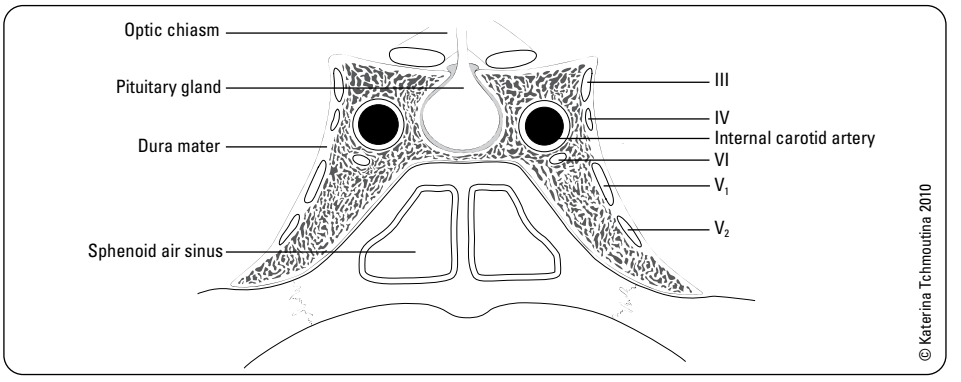



**Figure 11. Cavernous sinus (coronal view)**

**DDx of CN III Palsy**

**iCAM**
**i**schemic
**C**avernous sinus
**A**neurysm (PComm, internal carotid)
**M**idbrain lesion

# CN IV: Trochlear Nerve

### Clinical Features
- vertical and torsional diplopia; defect of intorsion and depression
- patient may complain of difficulty going down stairs or reading

### Differential Diagnosis
- common: ischemic (DM, HTN), idiopathic, trauma (TBI or surgical), congenital
- other: cavernous sinus lesion, superior orbital fissure (tumour, granuloma)

CN IV is the only cranial nerve that decussates at midline and exits posteriorly
A CN IV lesion may cause a contralateral deficit if lesion affects the nucleus

CN IV is at risk of trauma during neurosurgical procedures involving the midbrain because of its long intracranial course

# CN V: Trigeminal Nerve

### Clinical Features
- ipsilateral loss of facial sensation and corneal reflex, weakness of muscles of mastication (V3 only) with pterygoid deviation towards the side of the lesion

### Differential Diagnosis
- brainstem: ischemia, tumour, syringobulbia, demyelination
- peripheral: tumour, aneurysm, chronic meningitis, metastatic infiltration of nerve
- trigeminal ganglion: acoustic neuroma, meningioma, fracture of middle fossa
- cavernous sinus: carotid aneurysm, meningioma, sinus thrombosis
- trauma
- note: other CN V lesions that cause facial pain = trigeminal neuralgia, herpes zoster

**Distinguishing CN III, IV, and VI Lesions**

| | III | IV | VI |
|---|---|---|---|
| **Diplopia** | Oblique | Vertical | Horizontal |
| **Exacerbating** | Near target | Looking down | Far target |
| **Head Tilt** | Up and rotated away | Down and flexed away | Rotated towards |

Jaw deviation is towards the side of a LMN CN V lesion

# CN VI: Abducens Nerve

### Clinical Features
- resting inward deviation (esotropia)
- horizontal diplopia; defect of lateral gaze

### Differential Diagnosis
- pons (infarction, hemorrhage, demyelination, tumour): facial weakness and contralateral pyramidal signs
- tentorial orifice (compression, meningioma, trauma): false localizing sign of increased ICP
- cavernous sinus: carotid aneurysm, meningioma, sinus thrombosis
- ischemia of CN VI: DM, temporal arteritis, HTN, atherosclerosis
- congenital: Duane's syndrome

CN VI has the longest intracranial course and is vulnerable to increased ICP, creating a false localizing sign

# CN VII: Facial Nerve

### Clinical Features
- LMN lesion: ipsilateral facial weakness (facial droop, flattening of forehead, inability to close eyes, flattening of nasolabial fold)
- UMN lesion: contralateral facial weakness with forehead sparing (due to bilateral frontalis innervation)
- impaired lacrimation, decreased salivation, numbness behind auricle, hyperacusis, taste dysfunction of anterior 2/3 of tongue

### Differential Diagnosis
- idiopathic = Bell's palsy, 80-90% of cases (see Otolaryngology, OT22)
  - most often related to HSV, but other viruses may be implicated (CMV, herpes zoster, EBV)
- other: temporal bone fracture, EBV, Ramsay Hunt (VZV), otitis media/mastoiditis, sarcoidosis, DM mononeuropathy, parotid gland disease, Lyme meningitis, HIV

Forehead is spared in a UMN CN VII lesion due to bilateral innervation of CN VII nuclei from cerebral hemispheres for the frontalis

When screening for dysphagia and assessing aspiration risk, the presence of a gag reflex is insufficient; the correct screening test is to observe the patient drinking water from a cup while observing for any coughing, choking, or "wetness" of voice

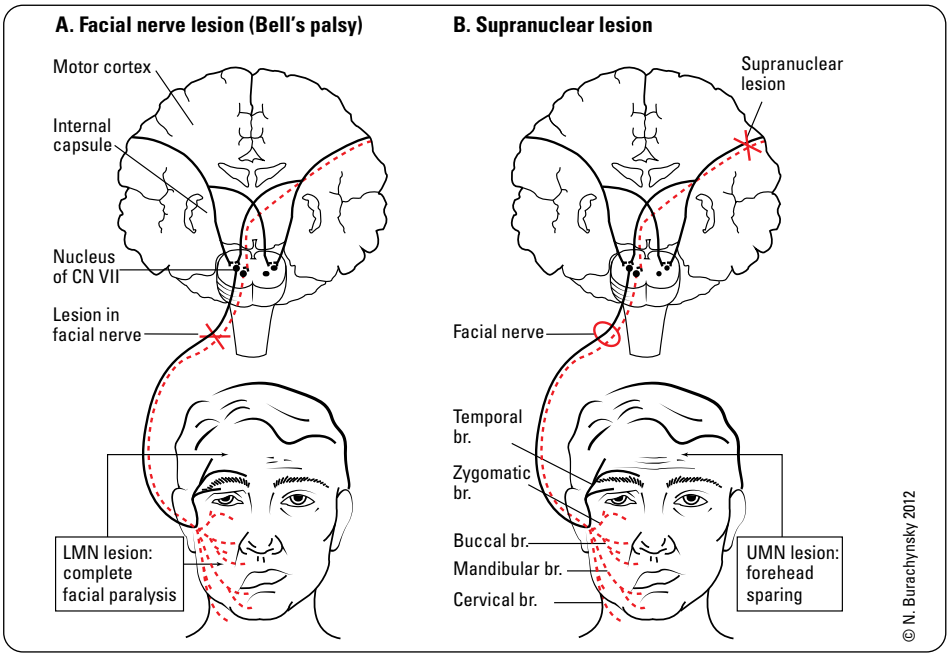



**Figure 12. UMN vs. LMN facial nerve palsy**

**Facial Nerve Branch Memory Aid**
**To Zanzibar By Motor Car**
**T**emporal
**Z**ygomatic
**B**uccal
**M**andibular
**C**ervical

**Differential Diagnosis of Lower Cranial Nerve Deficits (CN IX, X, XI, XII)**
**Intracranial/Skull Base**: meningioma, neurofibroma, metastases, osteomyelitis, meningitis
**Brainstem**: stroke, demyelination, syringobulbia, poliomyelitis, astrocytoma
**Neck**: trauma, surgery, tumours

Normal swallowing is initiated when the tongue moves a bolus back into the palatal archway. Tongue movements are innervated exclusively by CN XII. The bolus stimulates the soft palate to elevate and the bolus is deflected into the oropharynx. Next the pharyngeal constrictors contract, the larynx elevates, and the vocal cords close. Swallowing depends on afferent information via CN V, IX, and X and motor action via CN V, VII, IX, X, and XII. Connections in the nucleus of the tractus solitarius in the medulla (in proximity to the respiratory centre) act as the swallowing centre. Swallowing and breathing are coordinated to prevent aspiration

# CN VIII: Vestibulocochlear Nerve

- see Otolaryngology, OT14

# CN IX: Glossopharyngeal Nerve

### Clinical Features
- unilateral lesion is rare
- taste dysfunction in posterior 1/3 of tongue, absent gag reflex, and dysphagia

### Disorders
- glossopharyngeal neuralgia: sharp paroxysmal pain of posterior pharynx radiating to ear, triggered by swallowing
  - treated with carbamazepine or surgical ablation of CN IX

# CN X: Vagus Nerve

### Clinical Features
- oropharyngeal dysphagia (transfer dysphagia) due to palatal and pharyngeal weakness
- bulbar dysphagia (brainstem)
  - other causes of dysphagia: see Gastroenterology, G8
- dysarthria: inability to produce understandable speech due to impaired phonation and/or resonance

Uvula deviation is away from the side of a LMN CN X lesion due to impaired ipsilateral palatal elevation

# CN XI: Accessory Nerve

### Clinical Features
- LMN lesion: paralysis of ipsilateral trapezius and sternocleidomastoid (ipsilateral shoulder drop, weakness on turning head to contralateral side)
- UMN lesion: paralysis of ipsilateral sternocleidomastoid and contralateral trapezius

CN XI is vulnerable to damage during neck surgery

# CN XII: Hypoglossal Nerve

### Clinical Features
- LMN lesion: tongue deviation towards lesion; ipsilateral tongue atrophy and fasciculations (if chronic)
- UMN lesion: tongue deviation away from lesion; absence of atrophy and fasciculations

# Neuro-Ophthalmology

## Optic Neuritis

- see *Optic Disc Edema*, *Multiple Sclerosis*, N52

## Anterior Ischemic Optic Neuropathy (AION)

- see *Optic Disc Edema*
- non-arteritic (NAION): due to atherosclerosis
- arteritic (AAION): due to giant cell arteritis (see Rheumatology, RH21)

NAION can be caused by use of sildenafil (Viagra®) in rare cases

## Amaurosis Fugax

- see *Ophthalmology*, OP35 and *Stroke*, N48

## Optic Disc Edema

If you suspect the diagnosis of giant cell arteritis do not wait for biopsy results, begin treatment immediately

**Table 7. Common Causes of Optic Disc Edema**

| | Optic Neuritis | Papilledema | AION | CRVO |
|---|---|---|---|---|
| **Age** | <50 yr | Any | >50 yr but usually >70 yr | >50 yr |
| **Vision** | Rapidly progressive monocular central vision loss (↓ acuity and colour vision) with recovery | Late visual loss | Painless unilateral acute field defect over hours to days with ↓ colour vision | Painless unilateral variable vision loss |
| **Symptoms** | Pain (especially with eye movement) | H/A, N/V, local neurological deficits | If GCA: H/A, scalp tenderness, jaw claudication, weight loss, fatigue | Cardiovascular risk factors |
| **Pupil** | RAPD | No RAPD | RAPD | ± RAPD |
| **Fundus** | Disc swelling if anterior Normal disc if retrobulbar | Bilateral disc swelling, retinal hemorrhage, no venous pulsations | Pale segmental disc edema, retinal dot, flame hemorrhages | Swollen disc, venous engorgement, retinal hemorrhage |
| **Etiologies** | MS, viral | Increased ICP | Arteritic: giant cell arteritis Non-arteritic: atherosclerosis | Associated with vasculopathy, thrombus |
| **Investigations** | MRI with gadolinium | Emergent CT; LP if CT is normal to measure opening pressure | CBC, ESR, CRP, temporal artery biopsy | Fluorescein angiogram and coherence tomography |
| **Treatment** | IV methylprednisolone | Treat cause | Consider ASA if non-arteritic; steroids if arteritic | Optimize risk factors, reduce IOP, ± laser, ± VEGF inhibitors |

## Optic Disc Atrophy

- **etiologies:** glaucoma, AION, compressive tumour, optic neuritis, Leber's hereditary optic neuropathy, congenital
- **presentation:** disc pallor, low visual acuity, peripheral vision defect, decreased colour vision
- **treatment:** none (irreversible), aim to prevent

# Abnormalities of Visual Field

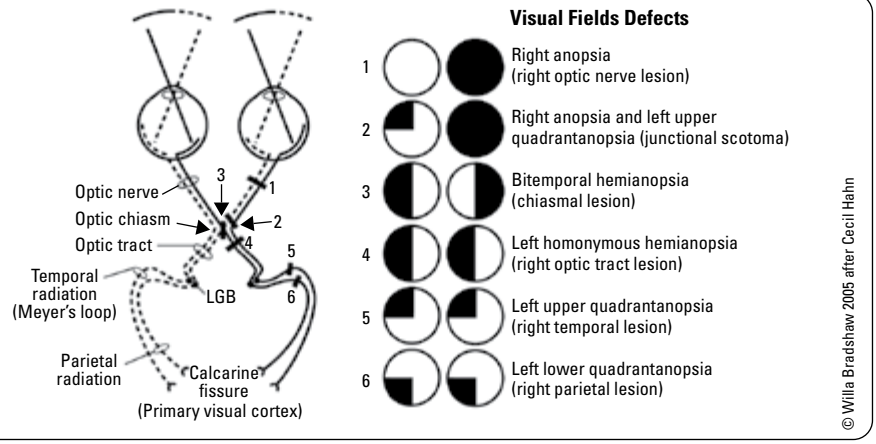



**Figure 13. Characteristic visual field defects with lesions along the visual pathway**

**Bitemporal Hemianopsia DDx by Age**
- Children: craniopharyngioma
- Middle aged (20s to 50s): pituitary mass
- Elderly (>60 yr): meningioma

In homonymous hemianopsia, more congruent deficits are caused by more posterior lesions; macular sparing may occur with occipital lesions

A lesion in a cerebral hemisphere causes eyes to "look away" from the hemiplegia, and to look towards the lesion
A lesion in the brainstem causes the eyes to "look toward" the side of the hemiplegia, and to look away from the lesion

Check all hemiplegic patients for homonymous hemianopsia (ipsilateral to side of hemiplegia)

# Abnormalities of Eye Movements

## Disorders of Gaze

### Pathophysiology
- horizontal gaze: FEF → contralateral PPRF (midbrain/pons) → eyes saccade away from FEF
- vertical gaze: cortex → rostral interstitial nucleus in the MLF (midbrain)

### Clinical Features
- unilateral lesion in one FEF → eyes deviate toward the side of the lesion
  - can be overcome with doll's eye maneuver
- unilateral lesion in the PPRF → eyes deviate away from the lesion
  - cannot be overcome with doll's eye maneuver if CN VI nucleus lesion as well
- seizure involving a FEF: eyes deviate away from the focus

### Etiology
- common: infarcts (frontal or brainstem), MS, tumours

## Internuclear Ophthalmoplegia

### Pathophysiology
- results from a lesion in the MLF which disrupts coordination between the CN VI nucleus in the pons and the contralateral CN III nucleus in the midbrain → disrupts conjugate horizontal gaze

### Clinical Features
- horizontal diplopia on lateral gaze, oscillopsia (objects in visual field appear to oscillate)
- gaze away from the side of the lesion: ipsilateral adduction defect and horizontal nystagmus in the contralateral, abducted eye
- cannot be overcome by caloric testing
- accommodation reflex intact
- may be bilateral (especially in MS)

### Etiology
- common: MS, brainstem infarct

### Investigations
- MRI

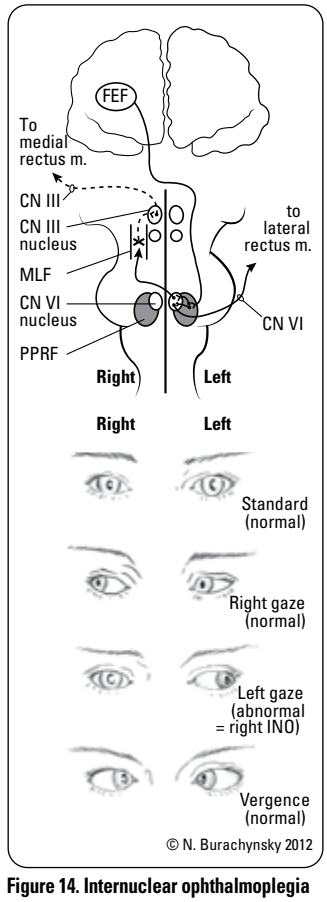



**Figure 14. Internuclear ophthalmoplegia**

# Diplopia

### Etiology – Monocular
- mostly due to benign optical problems (refractive error, cataract) or functional causes

### Etiology – Binocular (due to ocular misalignment)
- muscle: Graves' ophthalmopathy, EOM restriction/entrapment
- neuromuscular junction: MG (see *Myasthenia Gravis*, N38)
- cranial nerve palsy (see *Cranial Nerve Deficits*, N11)
- INO (see *Internuclear Ophthalmoplegia*, N15)
- other
  - orbital trauma (orbital floor fracture), tumour, infection, inflammation
  - Miller-Fisher variant of GBS
  - Wernicke's encephalopathy
  - leptomeningeal disease

### Approach to Diplopia
- monocular (diplopia when one eye open) vs. binocular (diplopia when both eyes open)
- horizontal vs. vertical vs. oblique diplopia
- direction of gaze that exacerbates diplopia
- corrective head movements

### Workup
- may observe isolated 4th or 6th nerve palsy for a few weeks, but workup if persistent or other symptoms develop
- indications for neuroimaging
  - bilateral or multiple nerve involvement
  - severe sudden onset headache (rule out aneurysm)

Diplopia worse at the end of the day suggests myasthenia gravis (e.g. fatigable)

If diplopia is only on extremes of gaze, cover each eye in isolation during extremes of gaze
The covered eye that makes the lateral image disappear is the pathological one

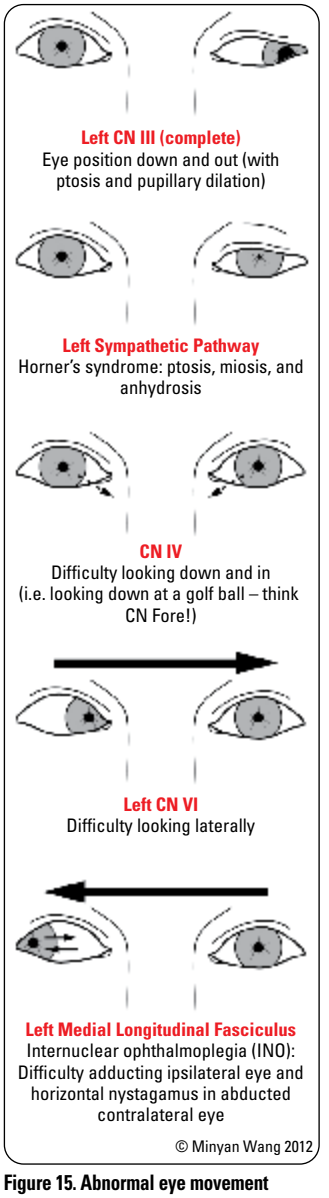



**Figure 15. Abnormal eye movement**

# Nystagmus

- rapid, involuntary, small amplitude movements of the eyes that are rhythmic in nature
- direction of nystagmus is labelled by the rapid component of the eye movement
- can be categorized by movement type (pendular, jerking, rotatory, coarse) or as physiological vs. pathological

**Table 8. Nystagmus Features**

| | Peripheral (Vestibular) | Central (Brainstem) |
|---|---|---|
| **Direction** | Unidirectional, fast phase away from the lesion | May be bilateral/unidirectional |
| **Nystagmus** | Usually horizontal ± rotatory | Usually vertical |
| **Gaze Fixation** | Relieves nystagmus | Does not relieve nystagmus |
| **Vertigo** | Severe | Mild |
| **Auditory Symptoms** | Common | Extremely rare |
| **Other Neurological Signs** | Absent | Often present |
| **DDx** | Benign paroxysmal positional vertigo, vestibular neuritis, Ménière's disease, toxicity, trauma, Ramsay Hunt syndrome | MS, vascular (brainstem/cerebellar), neoplastic/paraneoplastic |

# Abnormalities of Pupils

- see Ophthalmology, OP28

# Nutritional Deficiencies and Toxic Injuries

- sufficient nutritional intake is required for optimal nervous system functioning; deficiencies in the following key nutrients, among others, may impair central and peripheral nervous system function (potential neurological symptoms are provided)

**Table 9. Nutritional Deficiency Features and Management**

| Vitamin Deficiency | Neurological Clinical Manifestation | Investigation | Treatment* |
|---|---|---|---|
| **Vitamin B12** | Paresthesias and sensory ataxia are the most common initial symptoms<br>Myelopathy (Subacute Combined Degeneration), peripheral neuropathy<br>Neuropsychiatric: memory impairment, change in personality, delirium, and psychosis<br>Optic neuropathy | Serum cobalamin<br>Serum methylmalonic acid<br>Serum homocysteine | IM Vitamin B12 1000 µg for 5 d, then 1/mo or PO B12 1000 µg/d |
| **Folate** | Myelopathy, peripheral neuropathy<br>May be clinically indistinguishable from Vitamin B12 deficiency | Serum folate<br>Homocysteine | PO folate 1 mg tid initially; 1 mg daily thereafter |
| **Copper** | Myelopathy, pyramidal signs (e.g. brisk muscle stretch reflexes at the knees and extensor plantar responses)<br>Severe sensory loss | Serum copper and ceruloplasmin; urinary copper | Discontinue zinc; PO copper 8 mg/d for 1 wk; 6 mg/d for 1 wk; 4 mg/d for 1 wk; 2 mg/d thereafter |
| **Vitamin E** | Ophthalmoplegia, retinopathy, spinocerebellar syndrome with peripheral neuropathy (with signs of cerebellar ataxia) | Serum vitamin E; ratio serum vitamin E to sum of cholesterol and triglycerides | Vitamin E 2200 mg/kg/d PO or IM |
| **Thiamine** | Three manifestations include: beriberi (dry and wet), infantile beriberi, Wernicke-Korsakoff syndrome<br>Alcoholism is a cause of reduced thiamine intake and deficiency | Clinical diagnosis; brain MRI | Thiamine 100 mg IV followed by 50-100 mg IV or IM until nutritional status stable |
| **Pyridoxine (Vitamin B6)** | Painful sensorimotor peripheral neuropathy | Serum pyridoxal phosphate | Pyridoxine 50-100 mg daily |
| **Niacin (Vitamin B3)** | Pellagra: Encephalopathy, dementia, coma, and peripheral neuropathy | Urinary excretion niacin metabolites | Nicotinic acid 25-50 mg daily PO or IM. When supplementing, be aware of "niacin flush" in some patients |

*IM = intramuscular; IV = intravenous; PO = by mouth (orally)

- also consider occupational neurotoxic syndromes secondary to exposure to pesticides, solvents, and metals. Encephalopathy, extrapyramidal features, neurodegenerative diseases, and peripheral neuropathy are commonly encountered. Onset and progression of neurological diseases should be temporally related to neurotoxin exposure. Main toxins associated with neurotoxicity are listed below

**Table 10. Selected Occupational Neurotoxic Syndromes**

| Toxin | Associated Occupations | Characteristic Neurological Findings |
|---|---|---|
| **Organic Solvents** | Printer, spray painters, industrial cleaners, paint or glue manufacturers, graphic industry, electronic industry, plastic industry | Nausea, H/A, concentration difficulty<br>Long-term exposure may lead to "chronic solvent-induced encephalopathy", characterized by mild-to-severe cognitive impairment |
| **Pesticides** (e.g. insecticides, fungicides, rodenticides, fumigants, herbicides) | Agricultural work, pesticide manufacturing and formulating employees, highway and railway workers, green house, forestry and nursery workers | Parkinson's disease risk increased by ~70% following pesticide exposure |
| **Heavy Metals** (e.g. lead, mercury, manganese, aluminum, arsenic) | Battery and metal production (e.g. solder, pipes), chemical and electronic application industries, steel manufacturing, welders, alloy workers, transportation, packaging, construction | **Lead:** delayed/reversed development, permanent learning disabilities, peripheral neuropathy, seizures, coma, death from encephalopathy (rare)<br>**Mercury:** psychiatric disturbances, ataxia, visual loss, hearing loss, tiredness, memory disturbances<br>**Manganese:** psychiatric symptoms, hallucinations ("manganese madness"), extrapyramidal features, dystonia, parkinsonism (manganism)<br>**Aluminum:** implicated in Alzheimer's pathogenesis<br>**Arsenic:** sleeplessness/sleepiness, irritability, H/A, spasms in muscle extremities and muscle fatigue |
| **Gases** (e.g. carbon dioxide, nitrous oxide, formaldehyde) | Anesthesia, disinfection, manufacture of illuminating gas and water-gas | Cognitive/behavioural and emotional symptoms, parkinsonian syndromes |

## Neurologic Complications due to Toxic Injuries Related to Bariatric Surgery

- deficiencies of both fat- and water-soluble vitamins may occur following malabsorptive bariatric surgery
- patients who have undergone malabsorptive surgery should be monitored for late metabolic complications and neurological manifestations

# Seizure Disorders and Epilepsy

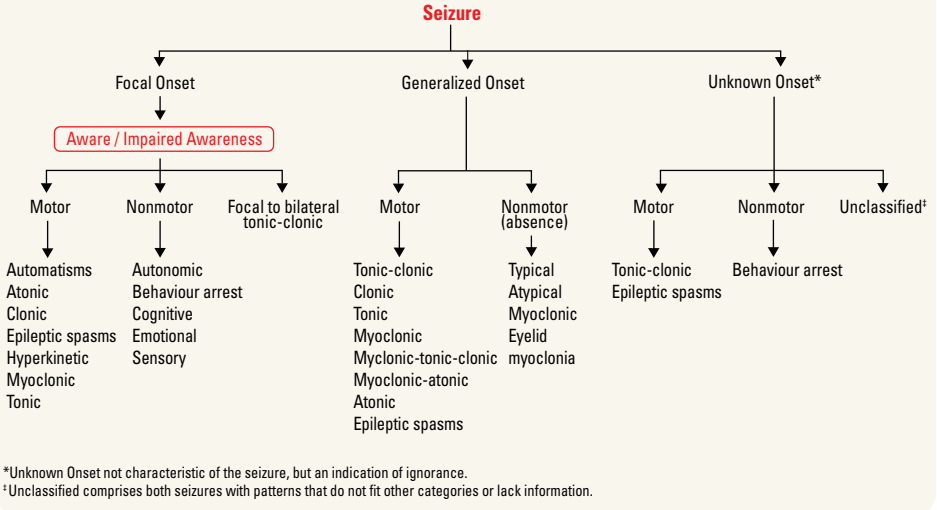
## Seizure

### Definitions

- seizure: transient occurrence of signs and/or symptoms due to abnormal hyper-synchronization of neurons
  - can be a symptom of acute insult to the brain such as: alcohol and illicit drug use/withdrawal, brain injury/abnormality (tumour, trauma, vascular), CNS infection, fever (children), metabolic (hypoglycemia, electrolyte abnormalities, liver/renal failure), medications, or be a genetic or inherited cause
- epilepsy: disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition.
  - diagnosis of an epilepsy syndrome requires:
    1) at least two unprovoked seizures occurring more than 24 hours apart
    2) one unprovoked seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) of two unprovoked seizures, occurring over the next 10 years
  - etiologies: genetic, structural (e.g. prior stroke, tumour, meningo/encephalitis, perinatal insult, vascular malformation, malformation of cortical development, neurodegenerative), or unknown

Stroke is the most common cause of late-onset (>50 yr) seizures, accounting for 50-80% of cases

### Classification




*Unknown Onset not characteristic of the seizure, but an indication of ignorance.
‡Unclassified comprises both seizures with patterns that do not fit other categories or lack information.

**Figure 16. Classification of seizures**

**Seizures and Dementia**
Neurodegenerative diseases can underlie seizures; conversely, seizures can be a cause of dementia

### Clinical Features

- **focal (partial) seizures**
  - focal can secondarily generalize, or remain focal
  - focal without impaired awareness (i.e. "simple partial seizures") → focal with impaired awareness (aka "complex partial seizures") → secondarily generalized seizures
  - **focal with intact awareness (simple partial)**
    - motor: dystonic posturing, clonic movements, forceful turning of eyes and/or head, focal muscle rigidity/jerking ± Jacksonian march (spreading to adjacent muscle groups)
    - sensory: unusual sensations affecting vision, hearing, smell, taste, or touch
    - autonomic: epigastric discomfort, pallor, sweating, flushing, piloerection, pupillary dilatation
  - **focal with impaired awareness (complex partial)**
    - patient may appear to be awake but with impairment of awareness
    - classic complex seizure is characterized by automatisms such as chewing, swallowing, lip-smacking, scratching, fumbling, running, disrobing, and other stereotypic movements
    - other forms: dysphasic, dysmnesic (déjà vu), cognitive (disorientation of time sense), affective (fear, anger), illusions, structured hallucinations (music, scenes, taste, smells), epigastric fullness
- **generalized seizures**
  - **absence (petit mal):** usually seen in children, unresponsive for 5-10 s with arrest of activity, staring, blinking or eye-rolling, no post-ictal confusion; 3 Hz spike and slow wave activity on EEG
  - **clonic:** whole body repetitive rhythmic jerking movements
  - **tonic:** whole body muscle rigidity in flexion or extension
  - **tonic-clonic (grand mal)**
    - may have prodrome of unease or irritability hours to days before
    - tonic ictal phase: muscle rigidity
    - clonic ictal phase: repetitive violent jerking of face and limbs, tongue biting, cyanosis, frothing, incontinence

**Temporal lobe epilepsy** is suggested by an aura of fear, olfactory or gustatory hallucinations, and visceral or déjà vu sensations
**Frontoparietal cortex seizures** are suggested by contralateral focal sensory or motor phenomena

**Antiepileptic Drug Monotherapy for Epilepsy: A Network Meta-analysis of Individual Participant Data**
Cochrane DB Syst Rev 2017;CD011412
Carbamazepine and lamotrigine are suitable first-line treatments for partial onset seizures with levetiracetam as a suitable alternative. Evidence supports sodium valproate as first-line treatment for generalized tonic-clonic seizures with lamotrigine and levetiracetam as suitable alternatives.

  - post-ictal phase: flaccid limbs, extensor plantar reflexes, headache, confusion, aching muscles, sore tongue, amnesia, elevated serum CK lasting hours; may have focal paralysis (Todd's paralysis)
- **myoclonic:** sporadic contractions localized to muscle groups of one or more extremities
- **atonic:** loss of muscle tone leading to drop attack

**Table 11. Classic Factors Differentiating Seizure, Syncope and Pseudoseizure**

| Characteristic | Seizure | Syncope | Pseudoseizure* (Psychogenic non-epileptic seizure) |
|---|---|---|---|
| **Timing** | Day or night (especially from sleep) | Day | Day; other people present |
| **Onset** | Sudden, in any position | Gradual; Upright position (not recumbent) | Provoked by emotional disturbance or suggestion |
| **Early Symptoms or Signs** | Possible specific aura | Lightheadedness, pallor, diaphoresis, tunnel vision | Variable |
| **Duration** | Brief or prolonged | Brief | Often prolonged |
| **Incontinence** | Common | Possible but rare | Rare |
| **Post-Ictal** | Confusion, aphasia, Todd's paresis, fatigue | No | Variable, often none |
| **Motor Activity** | Synchronous, stereotypic, automatisms (common in complex partial), lateral tongue biting, eyes open or eyes rolled back | Occasional brief jerks, can have "convulsive syncope" | Prolonged episodes, opisthotonos, eye closure, irregular extremity movements, shaking head, pelvic thrust, crying, tongue biting at the tip |
| **Injury** | Common | Rare unless from fall | Rare |
| **EEG** | Usually abnormal ± interictal discharges | Normal | Normal |

*Pseudoseizures do not rule out seizures (not uncommon to have both)

**DDx of Convulsions**
Syncope, pseudoseizure, hyperventilation, panic disorder, TIA, hypoglycemia, movement disorder, alcoholic blackouts, migraines (confusional, vertebrobasilar), narcolepsy (cataplexy)

Note that frontal seizures (rare) can look like a pseudoseizure due to odd motor activity that may occur

- alcoholic withdrawal seizures may occur up to 2 d from the last exposure to alcohol (see Emergency Medicine, ER54)

### Investigations
- CBC, electrolytes, fasting blood glucose, $Ca^{2+}$, $Mg^{2+}$, ESR, Cr, liver enzymes, CK, prolactin
- also consider toxicology screen, EtOH level, AED level (if applicable)
- CT/MRI (if new seizure without identified cause or known seizure history with new neurologic signs/symptoms)
  (Note: Neuroimaging may be normal in up to 90% of cases following the first unprovoked seizure)
- LP (if fever or meningismus)
- EEG (Note: EEG is specific but not sensitive)

By law, the Ministry of Transportation in most provinces must be contacted for all patients who have had a seizure; patients will have their license suspended until seizure free for 6 mo; commercial drivers face a longer wait

EEG findings suggestive of epilepsy: abnormal spikes, polyspike discharges, spike-wave complexes

51% of the EEGs within 24 h of the first seizure are positive in epilepsy. If the first routine EEG is normal, the yield of EEGs falls with each subsequent EEG, and thus a sleep EEG should be considered

### Treatment
- avoid precipitating factors
- indications for antiepileptic drugs (AED): EEG with epileptiform activity, remote symptomatic cause (organic brain disease, prior head injury, or CNS infection), abnormal neurologic examination or findings on neuroimaging, nocturnal seizure, recurrent unprovoked seizure
- psychosocial issues: stigma of seizures, education of patient and family, status of driver's license, pregnancy issues
- safety issues: driving, operating heavy machinery, bathing, swimming alone
- refer for evaluation for possible surgical treatment if focal and refractory

**Medical Emergency**: Status epilepticus can cause irreversible brain damage without treatment

## Status Epilepticus

- **definition:** medical emergency involving unremitting seizure or successive seizures without return to baseline state of >5 min
- **complications:** anoxia, cerebral ischemia and cerebral edema, MI, arrhythmias, cardiac arrest, rhabdomyolysis and renal failure, aspiration pneumonia/pneumonitis, death (20%)
- **initial measures:** ABCs, vitals, monitors, capillary glucose (STAT), ECG, nasal $O_2$, IV NS, IV glucose, IV thiamine, ABGs (if respiratory distress/cyanotic)
- **blood work:** electrolytes, $Ca^{2+}$, $Mg^{2+}$, $PO_4^{3-}$, glucose, CBC, toxicology screen, EtOH level, AED levels
- **focused history:** onset, past history of seizures, drug and alcohol ingestion, past medical history, associated symptoms, witnesses/collateral history
- **physical exam** (once seizures controlled): LOC, vitals, HEENT (nuchal rigidity, head trauma, tongue biting, papilledema), complete neurological exam, signs of neurocutaneous disorders, decreased breath sounds, cardiac murmurs or arrhythmias, urinary incontinence, MSK exam (rule out injuries)
- **post-treatment stabilization:** CT head, EEG, Foley catheter to monitor urine output, urine toxicology screen, monitor for rhabdomyolysis, and IV fluids to maintain normal cerebral perfusion pressure

The most common causes of status epilepticus are failure to take AEDs and first presentation of epilepsy
Despite being a common cause of seizures, EtOH withdrawal is a rare cause of status epilepticus

Rule out non-convulsive status epilepticus in any patient who is still unconscious >20 min post-ictal; order a stat EEG if unsure

Complex partial status epilepticus can resemble schizophrenia or psychotic depression

### Antiepileptic Drugs

- focal and most generalized seizures
  - valproate (Depakene®), lamotrigine (Lamictal®), levetiracetam (Keppra®), topiramate (Topamax®), phenobarbital (Phenobarb®), primidone, zonisamide, rufinamide (Banzel®), felbamate, benzodiazepines
- primarily focal seizures (± 2° generalization)
  - carbamazepine (Tegretol®), phenytoin (Dilantin®), gabapentin (Neurontin®), lacosamide (Vimpat®), oxcarbazepine (Trileptal®), eslicarbazepine acetate (Aptiom®), pregabalin (Lyrica®), tiagabine (Gabitril®), vigabatrin (Sabril®)
- absence seizure: ethosuximide (Zarontin®)

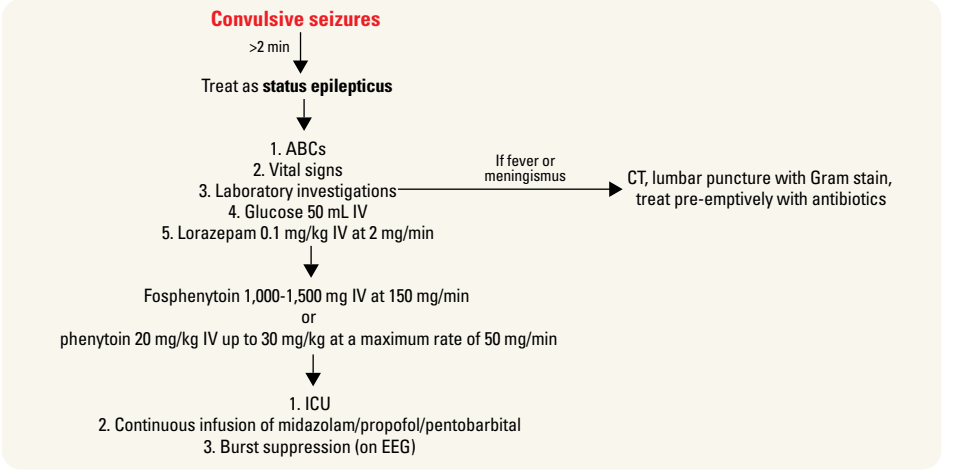



**Figure 17. Status epilepticus treatment algorithm**



Teratogenicity of anticonvulsants includes neural tube defects, cleft palate, urogenital malformations, and heart defects. Advise patient planning pregnancy to take 1-4 mg/d of folic acid. Optimize AEDs with lowest possible dose associated with good seizure control, preferably monotherapy if possible. The risk of fetal malformations with AEDs is 2x the general population; highest risk associated with valproic acid and/or 2+ concurrent AEDs. Consider pre-conception AED levels if patient is well-controlled, monthly serum levels during pregnancy, and titrate AED to maintain pre-conception serum levels. Refer to high risk OB for intrapartum fetal screening

# Behavioural Neurology

- see Psychiatry, PS22

## Acute Confusional State/Delirium

**Table 12. Selected Intracranial Causes of Acute Confusion**

| | Etiology | Key Clinical Features | Investigations |
|---|---|---|---|
| **Vascular** | Subarachnoid hemorrhage | Thunderclap H/A, increased ICP, meningismus, loss of consciousness | CT, LP<br>Angiography if CT and LP negative |
| | Stroke/TIA | Focal neurological signs | CT, MRI |
| **Infectious** | Meningitis | Fever, H/A, nausea, photophobia, meningismus | CT, LP |
| | Encephalitis | Fever, H/A, ± seizure<br>Focal neurological signs | CT, LP<br>MRI |
| | Abscess | Increased ICP<br>Focal neurological signs | CT with contrast (often ring enhancing lesion) |
| **Traumatic** | Diffuse axonal shear, epidural hematoma, SDH | Trauma Hx<br>Increased ICP<br>Focal neurological signs | CT<br>MRI |
| **Autoimmune** | Acute CNS vasculitis | Skin rash, active joints | ANA, ANCA, RF<br>MRI<br>Angiography |
| | Paraneoplastic encephalitis (anti-NMDA-R) | Onset: psychiatric features, memory loss, seizures<br>Delayed: movement disorder, and changes in BP, HR, and temperature | Serum and CSF (test for presence of antibodies), search for primary neoplasm |
| **Neoplastic** | Mass effect/edema, hemorrhage, seizure | Increased ICP<br>Focal neurological signs<br>Papilledema | CT<br>MRI<br>Search for primary neoplasm if metastatic disease |
| **Seizure** | Status epilepticus | See *Seizure Disorders and Epilepsy*, N18 | EEG |
| **Primary Psychiatric** | Psychotic, mood, and anxiety disorder | No organic signs or symptoms | No specific tests |

**Table 12. Selected Intracranial Causes of Acute Confusion** (continued)

| | Etiology | Key Clinical Features | Investigations |
|---|---|---|---|
| **Other** | Drugs (e.g. cocaine) | Chest pain, cough with black sputum, new-onset seizure, HTN, increased ICP, dyspnea | Vital signs<br>Serum chemistry and electrolyte analysis |
| | Medications (with anticholinergic side effects) | Flushing, dry skin and mucous membranes, mydriasis with loss of accommodation | Serum chemistry and electrolyte analysis |
| | Neuroleptic Malignant Syndrome | Antipsychotic medication use<br>Muscle rigidity<br>Hyperthermia<br>Autonomic instability | Serum chemistry and electrolyte analysis |

# Mild Neurocognitive Disorder (Mild Cognitive Impairment)

## Definition
- cognitive changes with measurable deficits in one or more cognitive domain
- preservation of independence or minimal impairment in ADLs and IADLs and not meeting criteria for major NCD
- amnestic (precursor to AD) vs. non-amnestic

## Epidemiology
- mild NCD: 2-10% at age 65 yr and 5-25% by age 85 yr

## Risk Factors
- vascular: hypertension, diabetes mellitus, obesity, cardiac disease, apolipoprotein E epsilon 4 genotype

## Clinical Features
- cognitive impairment with different subtypes
  - single domain vs. multiple domains (e.g. memory, visual spatial function, attention, executive function)
  - amnestic (memory impairment) vs. nonamnestic (memory function preserved)
  - amnestic subtype is the most common and most associated with AD pathology
  - important to ascertain that memory complaints represent change from baseline
- neuropsychiatric symptoms: depression (50%), irritability, anxiety, aggression, and apathy

## Investigations
- establish a baseline for follow-up
- clinical interview with patient and caregivers is the cornerstone of mild NCD evaluation
- neuropsychological testing
  - MMSE (not sensitive to early cognitive change) or MoCA (more sensitive, score <26 is impaired); should not be used in isolation
  - if abnormal, follow-up in one year to monitor cognitive and functional decline
- neuroimaging
  - role uncertain; a non-contrast brain CT is often ordered to evaluate for structural abnormalities (CVD, SDH, NPH, or mass lesion)
- other testing to exclude treatable conditions and underlying psychiatric conditions

## Treatment
- non-pharmacologic management: exercise training for 6 mo is likely to improve cognition; insufficient evidence to support or refute cognitive intervention, it may improve outcome on select cognitive measures
- no evidence for cholinesterase inhibitors, anti-inflammatory agents, vascular risk factor modification

## Prognosis
- development of major NCD for age ≥65 is 14.9% after 2 yr
- relative risk of major NCD is 3.3 after 2-5 yr

# Major Neurocognitive Disorder (formerly Dementia)

- see Psychiatry, PS23

## Definition
- acquired, generalized, and (usually) progressive impairment of cognitive function associated with impairment in ADLs/iADLs (i.e. shopping, food preparation, finances, medication management)
- diagnosis of major NCD requires presence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
  A) concern of the individual or a knowledgeable informant AND
  B) substantial impairment in cognitive performance either documented by standardized neuropsychological testing, or quantified clinical assessment



Delirium is a medical emergency carrying significant risk of morbidity and mortality; it is characterized by acute onset, disorientation, fluctuating level of consciousness, poor attention, and marked psychomotor changes



Visual hallucinations more commonly indicate organic disease



**Prevalence of Depression in Patients with Mild Cognitive Impairment: A Systematic Review and Meta-Analysis**
JAMA Psychiatry 2017;74(1):58-67
**Objectives**: To estimate the prevalence of depression in individuals with mild cognitive impairment.
**Methods**: Review of articles with patients with mild cognitive impairment as a primary study group, reported depression/depressive symptoms using a validated tool, and reported the prevalence of depression in patients with mild cognitive impairment.
**Results**: Pooled prevalence of depression patients with mild cognitive impairment was 32% (95% CI 27-37%). Prevalence in community-based populations (25%, 95% CI 19-30) was significantly lower than clinic-based populations (40%, 95% CI 32-48).
**Conclusions**: Prevalence of depression in patients with mild cognitive impairment is high.

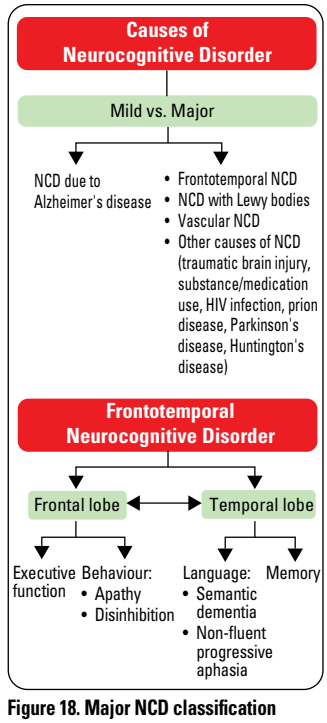



**Figure 18. Major NCD classification**

- see Psychiatry, PS23 for DSM-5 diagnostic criteria
- in comparison, mild NCD does not affect ADLs
  - mild NCD represents an intermediate stage between major NCD and normal aging

## Epidemiology
- major NCD: 1-2% at age 65 yr and reaching as high as 30% by age 85 yr
- major NCD due to Alzheimer's disease is uncommon before age 60 yr
- major NCD due to frontotemporal lobar degeneration has an earlier onset and represents a progressively smaller fraction of all NCDs with increasing age

## Etiology
- see Table 13
- reversible causes: alcohol (intoxication or withdrawal, Wernicke's encephalopathy), medication (benzodiazepines, anticholinergics), heavy metal toxicity, hepatic or renal failure, B12 deficiency, glucose, cortisol, thyroid dysfunction, normal pressure hydrocephalus (NPH), depression (pseudodementia), intracranial tumour, SDH, hypercalcemia (secondary to elevated PTH)
- must rule out delirium

## History
- "geriatric giants"
  - confusion/incontinence/falls
  - memory and safety (wandering, leaving doors unlocked, leaving stove on, losing objects, driving)
  - behavioural (mood, anxiety, psychosis, suicidal ideation, personality changes, aggression)
  - polypharmacy and compliance (sedative hypnotics, antipsychotics, antidepressants, anticholinergics)
- ADLs and IADLs
- cardiovascular, endocrine, neoplastic, renal ROS, head trauma history
- alcohol, smoking
- collateral history

## Physical Exam
- blood pressure
- hearing and vision
- neurological exam with attention to signs of parkinsonism, UMN findings
- general physical exam with focus on CVD, patient-specific risk factors, and history
- MMSE or MoCA, clock drawing, frontal lobe testing (go/no-go, word lists, similarities, proverb)

## Investigations
- rule out reversible causes
  - CBC (note MCV for evidence of alcohol use and B12 deficiency), glucose, TSH, B12, RBC folate
  - electrolytes, LFTs, renal function, lipids, serum calcium
  - CT head, MRI as indicated, SPECT (optional)
  - as clinically indicated: VDRL, HIV, ANA, anti-dsDNA, ANCA, ceruloplasmin, copper, cortisol, toxicology, heavy metals
- issues to consider
  - failure to cope, fitness to drive, caregiver capacity and wellbeing, power of attorney, legal will, advanced medical directives, patient and caregiver safety

**Table 13. Selected Causes of Major NCD (Dementia)**

| Etiology | Key Clinical Features | Investigations |
|---|---|---|
| **PRIMARY DEGENERATIVE** | | |
| Alzheimer's disease | Memory impairment<br>Aphasia, apraxia, agnosia | CT or MRI, SPECT |
| Dementia with Lewy bodies | Visual hallucinations<br>Parkinsonism<br>Fluctuating cognition | CT or MRI, SPECT |
| Frontotemporal dementia (e.g. Pick's disease) | Behavioural presentation: disinhibition, perseveration, decreased social awareness, mental rigidity, memory relatively spared<br>Language presentation: progressive non-fluent aphasia, semantic dementia | CT or MRI, SPECT |
| Huntington's disease | Chorea | Genetic testing |
| **VASCULAR** | | |
| Vascular cognitive impairment (previously Multi-infarct dementia) | Bradyphrenia without features of parkinsonism (slow thinking, slow rate of learning, slow gait)<br>Dysexecutive syndrome<br>May be abrupt onset<br>Stepwise deterioration is classic but progressive deterioration is most common | CT or MRI, SPECT |
| CNS vasculitis | Systemic signs and symptoms of vasculitis | ANA; ANCA; RF<br>CT or MRI<br>Angiography |

**Sensitivity and Specificity**

| Tool | Sensitivity | Specificity |
|---|---|---|
| MMSE | 87% | 82% |
| Clinical Judgment | 85% | 82% |
| DSM IV | 76% | 80% |

**Vitamin $B_{12}$ Deficiency Symptoms**
- Macrocytic anemia, pallor, SOB, fatigue, chest pain, palpitations
- Confusion or change in mental status (if advanced)
- Decreased vibration sense
- Distal numbness and paresthesia
- Weakness with UMN findings
- Diarrhea, anorexia

**Major NCD Considerations for Management**

**ABCDs**
**A**ffective disorders, **A**DLs
**B**ehavioural problems
**C**aretaker, **C**ognitive medications and stimulation
**D**irectives, **D**riving
**S**ensory enhancement (glasses/hearing aids)

**Most Common Causes of Rapidly Progressive Neurodegenerative Dementia (Less than 4 yr Survival): CJD, Frontal Temporal Lobar Dementia, Tauopathies, Diffuse Lewy Body Disease, and AD**
*Arch Neurol* 2009;66:201-207
Head turning sign: when patient is looking at his/her caregiver for answers after being asked a question in clinical interviews
60% sensitivity, 98% specificity for diagnosis of cognitive Impairment

| Early Signs of Major NCD | Normal Aging |
|---|---|
| Forgetting the names of close relations | Forgetting the names of acquaintances |
| Increased frequency of forgetting | Briefly forgetting part of an experience |
| Repeating phrases/ stories in the same conversation | Not putting away things properly |
| Unpredictable mood changes | Mood changes in response to appropriate causes |
| Decreased interest in activities and difficulty making choices | Changes in usual interests |

**Table 13. Selected Causes of Major NCD (Dementia)** (continued)

| Etiology | Key Clinical Features | Investigations |
|---|---|---|
| **INFECTIOUS** | | |
| Chronic meningitis | Fever, H/A, nausea<br>Meningismus<br>Localizing neurological deficits | CT, LP |
| Chronic encephalitis | Fever, headache | CT or MRI |
| Chronic abscess | Increased ICP<br>Localizing neurological deficits | CT with contrast |
| HIV | See Infectious Diseases, ID27 | HIV serology |
| Creutzfeldt-Jakob disease | Rapidly progressive, myoclonus | EEG, CT or MRI, LP |
| Syphilis | Ataxia, myoclonus, tabes dorsalis | LP, CT, or MRI<br>VDRL |
| **TRAUMATIC** | | |
| Diffuse axonal shear, epidural hematoma, subdural hematoma | Trauma Hx<br>Increased ICP, papilledema<br>Localizing neurological signs | CT |
| **RHEUMATOLOGIC** | | |
| SLE | See Rheumatology, RH11 | MRI<br>ANA, anti-dsDNA |
| **NEOPLASTIC** | | |
| Mass effect/edema, hemorrhage, seizure<br>Paraneoplastic encephalitis | Increased ICP<br>Localizing neurological signs<br>Systemic symptoms of cancer | CT with contrast<br>MRI<br>Paraneoplastic antibodies |
| **OTHER** | | |
| Normal pressure hydrocephalus | Gait disturbances<br>Urinary incontinence<br>See Neurosurgery, NS9 | CT or MRI |

**Cholinesterase Inhibitors for Dementia with Lewy Bodies (DLB), Parkinson's Disease Dementia (PDD) and Cognitive Impairment in Parkinson's Disease (CIND-PD)**
Cochrane DB Syst Rev 2012;3:CD006504
**Study**: Meta-analysis of RCTs assessing efficacy of treatment with cholinesterase inhibitors in DLB, PDD, and CIND-PD.
**Results**: The six trials (n=1236) included demonstrated therapeutic benefit of cholinesterase inhibitors for global assessment, cognitive function, behavioural disturbance, and activities of daily living. Cholinesterase inhibitors were associated with increased adverse events (OR 1.64) and drop out (OR 1.94). Adverse events were more common with rivastigmine but not with donepezil. Fewer deaths occurred in the treatment group (OR 0.28).
**Conclusion**: Current evidence supports use of cholinesterase inhibitors for patients with PDD but its role in DLB and CIND-PD is still unclear.

# Major or Mild NCD due to Alzheimer's Disease

- see Psychiatry, PS24

## Definition

- beyond criterion for NCD, the core features of Alzheimer's disease include an insidious onset and gradual progression of cognitive and behavioural symptoms
- typical presentation: amnestic
  - mild phase: impairment in memory and learning sometimes accompanied with deficits in executive function
  - moderate-severe phase: visuoconstructional/perceptual-motor ability and language may also be impaired
  - social cognition tends to be preserved until late in the course of the disease
- atypical nonamnestic presentation (one of the following):
  1. aphasia: language disturbance
  2. apraxia: impaired ability to carry out motor activities despite intact motor function
  3. agnosia: failure to recognize or identify objects despite intact sensory function

**4 As and one D of AD**
**A**nterograde amnesia
**A**phasia
**A**praxia
**A**gnosia
**D**isturbance in executive function
(Anterograde amnesia plus at least one of the other features is required for AD diagnosis)

## Pathophysiology

- genetic factors
  - minority (<1%) of AD cases are familial (autosomal dominant), associated with early onset AD (<65 yr)
  - 3 major genes, responsible for 5-10% of early onset AD cases, for autosomal dominant AD have been identified:
    - amyloid precursor protein (chromosome 21), presenilin 1 (chromosome 14), presenilin 2 (chromosome 1)
    - the E4 polymorphism of apolipoprotein E (APOE) is a susceptibility genotype (E2 is protective)
    - note: APOE cannot serve as a diagnostic marker because it is only a risk factor and neither necessary nor sufficient for disease occurrence
- pathology (not necessarily specific for AD)
  - gross pathology
    - diffuse cortical atrophy, especially frontal, parietal, and temporal lobes (hippocampi)

Down syndrome predisposes to early onset of Alzheimer's (i.e. age of ~40) due to three copies of the amyloid gene (APP)

- microscopic pathology
  - senile amyloid beta plaques (extracellular deposits of amyloid in the grey matter of the brain)
  - loss of synapses
  - neurofibrillary tangles (intracytoplasmic paired helical filaments with amyloid and hyperphosphorylated Tau protein)
  - loss of cholinergic neurons in the nucleus basalis of Meynert that project diffusely throughout the cortex
- biochemical pathology
  - 50-90% reduction in action of choline acetyltransferase

## Epidemiology
- 1/12 of population 65-75 yr of age
- up to 1/3 population >85 yr of age
- very rare <65 yr of age
- accounts for 60-90% of all dementias (depending on setting and diagnostic criteria)

## Risk Factors
- age is the greatest risk factor
- genetic susceptibility polymorphism: apolipoprotein E4 increases risk and decreases age of onset
- other factors include: traumatic brain injury, family history, Down syndrome, low education, and vascular risk factors (e.g. smoking, HTN, hypercholesterolemia, DM)

## Clinical Features
- cognitive impairment
  - memory impairment for newly acquired information (early)
  - deficits in language, abstract reasoning, and executive function
- behavioural and psychiatric manifestations (80% of those with major NCD)
  - mild NCD: major depressive disorder and/or apathy
  - major NCD: psychosis, irritability, agitation, combativeness, and wandering
- motor manifestations (late)
  - gait disturbance, dysphagia, incontinence, myoclonus, and seizures

## Investigations
- perform investigations to rule out other potentially reversible causes of dementia
- EEG: usually normal in mild-moderate stages, slow waves in moderate-advanced stages. May observe generalized slowing (nonspecific)
- MRI: preferential atrophy of the hippocampi and precuneus of the parietal lobe; dilatation of lateral ventricles; widening of cortical sulci
- SPECT: hypoperfusion in temporal and parietal lobes
- PET imaging using Pittsburgh compound B (PIB) as a tracer enables imaging of beta-amyloid plaque in neuronal tissue
- LP: amyloid beta protein can be measured in CSF

## Treatment
- acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) slow the decline in cognitive function
- do not prolong life expectancy but reduce morbidity
- relative contraindications: bradycardia, heart block, arrhythmia, CHF, CAD, asthma, COPD, ulcers, or risk factors for ulcers and/or GI bleeding
- galantamine is contraindicated in patients with hepatic/renal impairment
- memantine is an NMDA-receptor antagonist that has some benefits in later stage AD (i.e. when MMSE <17)
- behavioural symptom management

1. pharmacologic
   - low dose neuroleptics for agitation (neuroleptics may worsen cognitive decline)
   - trazodone for sleep disturbance
   - antidepressants (SSRIs)
2. non-pharmacologic
   - redirection
   - explore inciting factors for behaviour and modify behaviour of patient or caregiver
   - family support and daycare facilities

## Prognosis
- mean duration of survival after diagnosis is approximately 10 yr, reflecting the advanced age of the majority of individuals rather than the course of the disease
- death commonly results from aspiration



**Cognitive Effects of Atypical Antipsychotic Medications in Patients with Alzheimer's Disease: Outcomes from CATIE-AD**
Am J Psychiatry 2011;168:831-839
**Study**: 421 outpatients with Alzheimer's disease and psychosis or agitated/aggressive behaviour were randomized to receive olanzapine, quetiapine, risperidone, or placebo in a multicentre double-blinded RCT. MMSE and Alzheimer's Disease Assessment Scale (ADAS) scores were measured at 36 wk.
**Results**: Patients receiving atypical antipsychotics exhibited a faster rate of cognitive decline as measured by MMSE scores (– 0.067/wk vs. -0.007/wk). They also had a significantly faster decline compared to placebo on a composite measure of ADAS, MMSE, and various other cognitive tests (-0.011/wk vs. -0.001/wk).
**Conclusions**: Long-term use of atypical antipsychotics for behavioural symptoms and psychosis in dementia patients is associated with greater rates of cognitive decline.

# Major or Mild NCD with Lewy Bodies (formerly Dementia with Lewy Bodies)

### Definition
- NCD characterized by progressive cognitive impairment (with early changes in complex attention and executive function) and recurrent complex visual hallucinations
- core diagnostic features
  - fluctuating cognition with pronounced variations in attention and alertness
  - recurrent visual hallucinations that are well formed and detailed
  - one or more spontaneous cardinal features of parkinsonism (bradykinesia, rest tremor, or rigidity), with onset subsequent to development of cognitive decline
  - rapid eye movement (REM) sleep behaviour disorder
- suggestive/supportive features
  - severe sensitivity to neuroleptic medications (rigidity, neuroleptic malignant syndrome, extrapyramidal symptoms)
  - repeated falls, syncope, or transient episodes of unexplained loss of consciousness
  - auditory or other nonvisual hallucinations, systematic delusions, and depression

### Etiology and Pathogenesis
- Lewy bodies (eosinophilic cytoplasmic inclusions) found in both cortical and subcortical structures
- mixed DLB and AD pathology is common

### Diagnostically Suggestive Markers
- low striatal dopamine transporter uptake on SPECT or PET
- relative preservation of medial temporal structures on CT/MRI

### Epidemiology
- 0.1-5% of the general elderly population
- Lewy bodies are present in 20-35% of all dementia cases (more common in males)

### Treatment
- acetylcholinesterase inhibitors (e.g. donepezil)

### Prognosis
- average duration of survival 5-7 yr

# Major or Mild Frontotemporal NCD (formerly Frontotemporal Dementia)

### Definition
- group of disorders caused by progressive cell degeneration in the brain's frontal or temporal lobes
  - deficits in executive function (e.g. poor mental flexibility, abstract reasoning, response inhibition, planning/organization, increased distractibility) with relative sparing of learning, memory, and perceptual-motor function
- "probable" is distinguished from "possible" frontotemporal NCD by:
  - evidence of causative frontotemporal NCD genetic mutation, from either family history or genetic testing
  - evidence of disproportionate frontal and/or anterior temporal atrophy on MRI or CT
  - evidence of frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

### Behavioural Variant FTD
- most common variant
- insidious onset: must show progressive deterioration of behaviour and/or cognition by observation or history
- typically early symptom presentation (i.e. within the first 3 yr)
- at least 3/5 of the following symptoms must be present and persistent/recurrent:
  - behavioural disinhibition (socially inappropriate behaviour, impulsive, careless)
  - apathy or inertia (decreased initiation or continuation of behaviour, requiring cues/prompts, less likely to initiate or sustain conversations)
  - loss of sympathy or empathy (diminished response to others' needs/feelings, social interest)
  - preservative, stereotyped, or compulsive/ritualistic behaviour
  - hyperorality and dietary changes (binge eating, increased consumption of alcohol/cigarettes or inedible objects)

### Language Variants (Primary Progressive Aphasia)
- prominent decline in language ability, in the form of speech production, word finding, object naming, grammar, or word comprehension
- three subtypes
  - nonfluent/agrammatic variant PPA (NFAV-PPA) or progressive nonfluent aphasia (PNFA): non-fluent, laboured articulation/speech, anomia, preserved single word comprehension, word-finding deficit, impaired repetition
  - semantic variant PPA (SV-PPA) or semantic dementia (SD): fluent, normal rate, anomia, impaired single word comprehension, intact repetition, use words of generalization ("thing") or supraordinate categories ("animal" for "dog")
  - logopenic progressive aphasia (LPA): naming difficulty and impaired repetition

### FTD Movement Disorders
- corticobasal degeneration (CBD) (see Parkinsonism)
- progressive supranuclear palsy (PSP) (see Parkinsonism)

### Etiology and Pathogenesis
- unknown, however there is likely a genetic/familial component (40% have family history of early onset NCD)
- genetic variants: MAPT gene (Tau), PGRN gene (progranulin), VCP gene, TARDBP gene (TDP-43), CHMP2D gene
- unlike AD, FTD does not show amyloid plaques or neurofibrillary tangles, instead it is characterized by severe atrophy and specific neuronal inclusion bodies
- gross changes: atrophy in the frontal and anterior temporal lobes; cortical thinning; possible ventricular enlargement
- histological changes: gliosis, swollen neurons, microvacuolation, inclusion bodies in neurons/glia (Tau or TDP-43)

### Epidemiology
- 4th most common cause of dementia (5% of all dementia cases)
- common cause of early-onset NCD in individuals younger than 65 yr

### Prognosis
- median survival being 6-11 yr after symptoms onset and 3-4 yr after diagnosis
- survival is shorter and decline is faster than in typical Alzheimer's disease

## Major or Mild Vascular NCD

### Definition
- diagnosis of major or mild NCD with determination of CVD as the dominant if not exclusive pathology that accounts for the cognitive deficits
- vascular etiology suggested by one of the following:
  - onset of cognitive deficits is temporally related to one or more cerebrovascular events
  - evidence for decline is prominent in complex attention (including processing speed) and frontal-executive function
- neuroimaging evidence of cerebrovascular disease comprises one or more of the following:
  - one or more large vessel infarct or hemorrhage
  - a strategically placed single infarct or hemorrhage (e.g. angular gyrus, thalamus, basal forebrain)
  - two or more lacunar infarcts outside the brainstem
  - extensive and confluent white matter lesions
- for mild vascular NCD: history of a single stroke or extensive white matter disease is sufficient
- for major vascular NCD: history of two or more strokes, a strategically placed stroke, or a combination of white matter disease and one or more lacunae is generally necessary
- associated features supporting diagnosis: personality and mood changes, abulia, depression, emotional lability, and psychomotor slowing

### Etiology and Pathogenesis
- major risk factors are the same as those for CVD (i.e. HTN, DM, smoking, obesity, high cholesterol levels, high homocysteine levels, other risk factors for atherosclerosis, atrial fibrillation, and conditions increasing risk of cerebral emboli)
- major or mild vascular NCD with gradual onset and slow progression is generally due to small vessel disease leading to lesions in white matter, basal ganglia, and/or thalamus
- cognitive deficits can be attributed to disruption of cortical-subcortical circuits

### Epidemiology
- second most common cause of NCD
- prevalence estimates for vascular dementia/NCD range from 0.2-13% (by age 70), 16% (ages ≥80) to 44.6% (ages ≥90)
- higher prevalence in African Americans
- prevalence higher in males than in females

# Creutzfeldt-Jakob Disease

- rare degenerative fatal brain disorder caused by prion proteins causing spongiform changes, astrocytosis, and neuronal loss
- most common forms are sporadic (85%), hereditary (5-10%), and acquired (<1%)
- investigations: CSF analysis, MRI brain (cortical (i.e. cortical ribbon sign) and/or subcortical (hockey stick sign) FLAIR changes), EEG (periodic complexes)
- definitive diagnosis is by brain biopsy
- no treatments currently exist

Prion proteins have a normal form and an infectious form, which results from conversion of the protein from α-helix (normal) to β-pleated sheet (abnormal); these abnormally folded proteins aggregate leading to neuronal loss

# Aphasia

## Definition

- an acquired disturbance of language characterized by errors in language production, writing, comprehension, or reading

## Neuroanatomy of Aphasia

- Broca's area (posterior inferior frontal lobe) is involved in language production (expressive)
- Wernicke's area (posterior superior temporal lobe) is involved in comprehension of language (receptive)
- angular gyrus is responsible for relaying written visual stimuli to Wernicke's area for reading comprehension
- arcuate fasciculus association bundle connects Wernicke's and Broca's areas

>99% of right-handed people have left hemisphere language representation

70% of left-handed people have left hemisphere language representation, 15% have right hemisphere representation, and 15% have bilateral representation

## Assessment of Language

- assessment of context
  - handedness (writing, drawing, toothbrush, scissors), education level, native language, learning difficulties
- assessment of aphasia
  - spontaneous speech (fluency, paraphasias, repetition, naming, comprehension – auditory and reading, writing, neologisms)

**Types of Paraphasias**
Semantic ("chair" for "table")
Phonemic ("clable" for "table")

Aphasia localizes the lesion to the dominant cerebral hemisphere

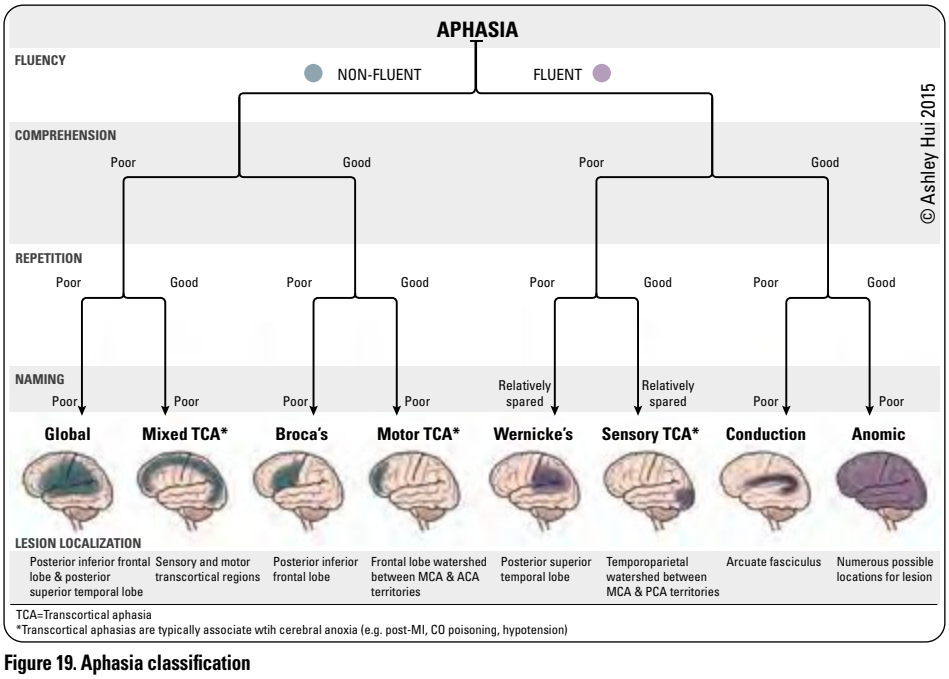



**Figure 19. Aphasia classification**

# Apraxia

## Definition
- inability to perform skilled voluntary motor sequences that cannot be accounted for by weakness, ataxia, sensory loss, impaired comprehension, or inattention

## Clinicopathological Correlations

**Table 14. Apraxia**

| | Description | Tests | Hemispheres |
|---|---|---|---|
| **Ideomotor** | Inability to perform skilled learned motor sequences | Blowing out a match, combing one's hair | Left |
| **Ideational** | Inability to sequence actions | Preparing and mailing an envelope | Right and left |
| **Constructional*** | Inability to draw or construct | Copying a figure | Right and left |
| **Dressing*** | Inability to dress | Dressing | Right |

*Refers specifically to the inability to carry out the learned movements involved in construction, drawing, or dressing; not merely the inability to construct, draw, or dress. Many skills aside from praxis are needed to carry out these tasks.

# Agnosia

## Definition
- inability to recognize the significance of sensory stimuli in the presence of intact sensation and naming

## Clinicopathological Correlations

**Table 15. Agnosias**

| | Description | Lesion |
|---|---|---|
| **Apperceptive Visual Agnosia** | Inability to name or demonstrate the use of an object presented visually 2° to distorted visual perception<br>Recognition by touch remains intact | Bilateral temporo-occipital cortex |
| **Associative Visual Agnosia** | Inability to name an object presented visually 2° to disconnect between visual cortex and language areas<br>Visual perception is intact as demonstrated by visual matching | Bilateral inferior temporo-occipital junction |
| **Prosopagnosia** | Inability to recognize familiar faces in the presence of intact visual perception and intact auditory recognition | Bilateral temporo-occipital areas or right inferior temporo-occipital region |
| **Colour Agnosia** | Inability to perceive colour | Bilateral inferior temporo-occipital lesions |
| **Impaired Stereognosis** | Inability to identify objects by touch | Anterior parietal lobe in the hemisphere opposite the affected hand |
| **Finger Agnosia** | Inability to recognize, name, and point to individual fingers | Dominant hemisphere parietal-occipital lesions |



**Parietal Lobe Lesions**
- Lesions of the dominant parietal lobe are characterized by Gerstmann's syndrome: acalculia, agraphia, finger agnosia, and left-right disorientation
- Lesions of the non-dominant parietal lobe are characterized by neglect, anosognosia, and asomatognosia
- Cortical sensory loss (graphesthesia, astereognosis, impaired 2 point discrimination, and extinction) can be seen with left or right parietal lesions

# Mild Traumatic Brain Injury

## Definition
- mild TBI = concussion
- trauma-induced transient alteration in mental status that may involve loss of consciousness
- hallmark symptoms: confusion and amnesia, which may occur within minutes
- loss of consciousness (if present) less than 30 min, initial GCS between 13-15, post-traumatic amnesia <24 h



- Extent of retrograde amnesia correlates with severity of injury
- Regained from most distant to recent memories

## Epidemiology
- 75% of TBIs are estimated to be mild; the remainder are moderate or severe (see Neurosurgery, NS32 and Emergency Medicine, ER8)
- highest rates in children 0-4 yr, adolescents 15-19 yr, and elderly >65 yr

## Clinical Features
- impairments following mild TBI
  - somatic: headache, sleep disturbance, nausea, vomiting, and blurred vision
  - cognitive dysfunction: attentional impairment, reduced processing speed, drowsiness, amnesia
  - emotion and behaviour: impulsivity, irritability, depression
- severe concussion: may precipitate seizure, bradycardia, hypotension, sluggish pupils
- associated conditions: brain contusion, diffuse axonal injury, C-spine injury

### Investigations
- neurological exam to identify focal neurologic deficits
- neurocognitive assessment
  - simple orientation questions are inadequate to detect cognitive changes
  - initial assessment of severity is determined by Glasgow Coma Scale
    - mild: 13-15, moderate: 9-12, severe: 3-8
  - sideline evaluation: Standardized Assessment of Concussion, Westmead Post-Traumatic Amnesia Scale, Sport Concussion Assessment Tool
- neuroimaging
  - x-ray skull: not indicated for routine evaluation of mild TBI
  - CT head as indicated by Canadian CT Head Rules
  - MRI not indicated in initial evaluation; consider if continued or worsening symptoms despite normal CT

### Treatment
- observation for first 24 h after mild TBI because of risk of intracranial complications
- emergency department for assessment if any loss of consciousness or persistent symptoms
- hospitalization with normal CT if GCS <15, seizures, or bleeding diathesis; or abnormal CT scan
- early rehabilitation to maximize outcomes
  - OT, PT, SLP, vestibular therapy, driving, therapeutic recreation
- pharmacological management of headaches, pain, depression
- CBT, relaxation therapy
- follow Return to Play guidelines (www.thinkfirst.ca)

### Prognosis
- most recover from mild TBI with minimal treatment, but some experience long-term consequences
- patients with a previous concussion are at increased risk of subsequent concussion and cumulative brain injury
- repeat TBI can lead to life threatening cerebral edema (controversially known as second impact syndrome) or permanent impairment
- sequelae include:
  - post-concussion syndrome: dizziness, headache, neuropsychiatric symptoms, cognitive impairment (usually resolves within weeks to months)
  - post-traumatic headaches: begin within 7 d of injury
  - post-traumatic epilepsy: approximately 2% risk post-mild TBI; prophylactic anticonvulsants are not effective
  - post-traumatic vertigo

# Neuro-Oncology

## Paraneoplastic Syndromes

- see Endocrinology, E51

## Tumours of the Nervous System



- see Neurosurgery, NS11

# Movement Disorders

## Function of the Basal Ganglia

- the cerebral cortex initiates movement via excitatory (glutamatergic) projections to the striatum, where they then activate two pathways: direct and indirect
  - direct: cortex activates the thalamus, allowing movement
  - indirect: inhibits the thalamus and preventing movement

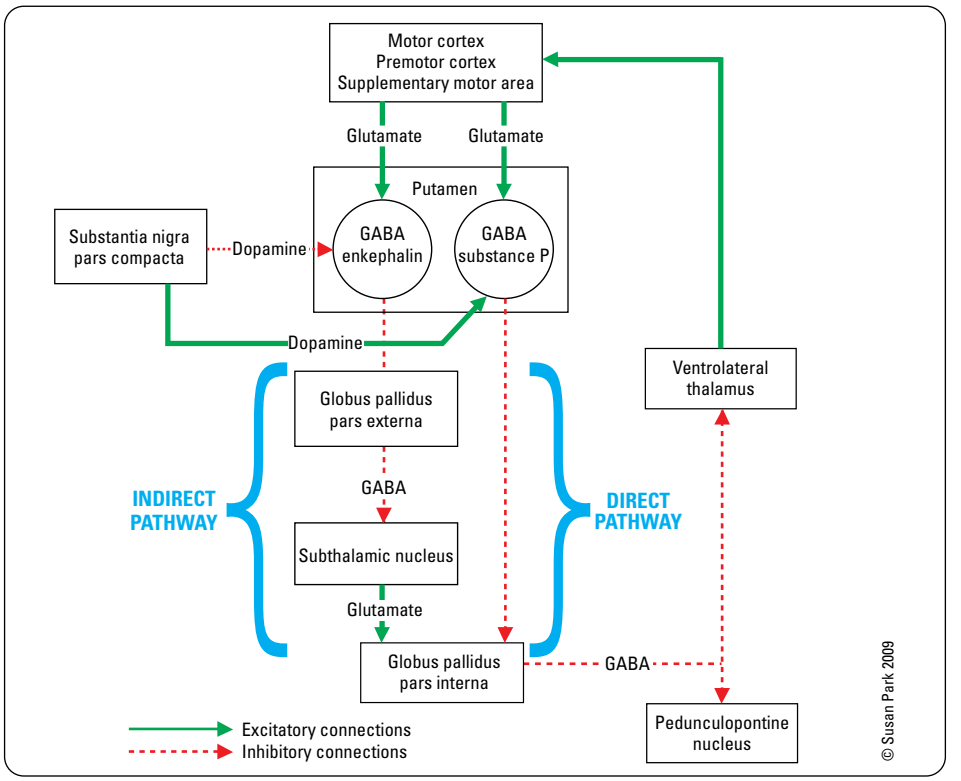



**Figure 20. Neural connections of the basal ganglia**

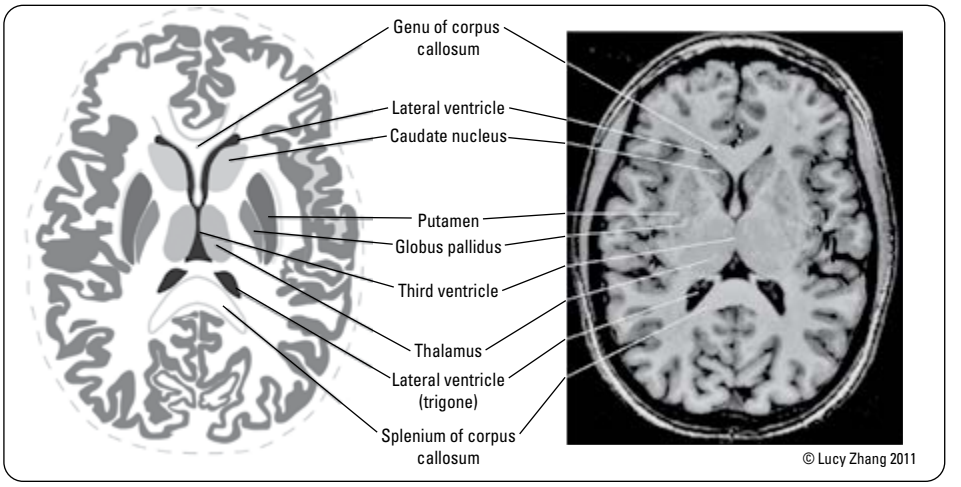



**Figure 21. Horizontal section of basal ganglia**

# Overview of Movement Disorders

**Table 16. Movement Disorder Definitions**

| | |
|---|---|
| **Akathisia** | Subjective generalized restlessness relieved by voluntary stereotypic movements (e.g. squirming) |
| **Asterixis** | Transient loss of muscle tone (negative myoclonus) |
| **Athetosis** | Slow writhing movements, especially distally |
| **Bradykinesia** | Slow and/or small amplitude of movements |
| **Chorea** | Brief, unpredictable, irregular movements, flowing from one body part to another; can appear purposeful in milder forms |
| **Dysdiadochokinesia** | Inability to smoothly perform rapidly alternating movements |
| **Dyskinesia** | Any involuntary movement, but the term is often used to describe the stereotypical movements that come with long-term neuroleptic use (tardive dyskinesia) |
| **Dystonia** | Co-contraction of agonist and antagonist muscles causing sustained twisting movements which can be tonic (dystonic postures) or phasic (dystonic movements) |
| **Freezing** | Episodes of halted motor action, especially during repetitive actions (e.g. walking) |
| **Ballism** | Large-amplitude, involuntary, flinging movements that are most commonly unilateral (hemiballism) |
| **Myoclonus** | Brief muscle group contraction that is either focal, segmental, or generalized |
| **Myokymia** | Spontaneous, fine, fascicular contraction of muscle |
| **Tachykinesia** | Acceleration of movements e.g. accelerated walking (festination) |
| **Tics** | Stereotyped and brief repetitive actions due to inner urge<br>Can be suppressed<br>Can be phonic (vocal) or motor |
| **Tremor** | Rhythmic and involuntary antagonistic muscle contractions |

In some cases, dystonias may occur only during voluntary movement and sometimes only during specific activities, such as writing, chewing, or speaking (task-specific dystonia)

Hemiballismus is most often due to a vascular lesion of the contralateral subthalamic nucleus

Myoclonus is often stimulus-sensitive as it can be induced by sudden noise, movement, light, visual threat, or pinprick

# Movement Disorders

## Differential Diagnoses

### 1. Tremor

**Table 17. Approach to Tremors**

| | Resting | Action-Postural | Action-Intention |
|---|---|---|---|
| **Body Part** | UE>jaw>LE>head | UE>head>LE>tongue | UE>voice>LE |
| **Characteristics** | 3-7 Hz pill rolling | 6-12 Hz fine tremor | <5 Hz coarse tremor |
| **Worse with Associated Sx** | Rest while concentrating<br>"TRAP" | Sustained posture (outstretched arms)<br>± Autosomal dominant FHx | Finger to nose<br>Cerebellar findings |
| **DDx** | PD, Parkinsonism, Wilson's disease, mercury poisoning | Physiologic, essential, hyperthyroidism, hyperglycemia, heavy metal poisoning, CO poisoning, drug toxicity, sedative/alcohol withdrawal | Cerebellar disorders, Wilson's disease, MS, anticonvulsants, alcohol, sedatives |
| **Treatment** | Carbidopa-levodopa (Sinemet®), surgery, DBS | Propranolol, primidone, topiramate, and other anticonvulsants | Treat underlying cause |

In a young patient (<45) must do TSH (thyroid disease), ceruloplasmin (Wilson's disease), and CT/MRI (cerebellar disease) as indicated by type of tremor

Most of the time, essential tremor does not need treatment

**Alcohol**
- Dampens essential tremor
- Potentiates intention tremor during abstinence (delirium tremens)
- Does not improve resting tremor of PD

**2. Chorea:** Huntington's disease (HD), HD-like syndromes, neuroacanthocytosis, SLE, APLA syndrome, Wilson's disease, CVD, tardive dyskinesia, senile chorea, Sydenham's chorea, pregnancy chorea (chorea gravidarum)

Most common cause of chorea is drug therapy for PD (levodopa induced dyskinesias)

**3. Dystonia**
- **primary dystonia**: familial, sporadic (torticollis, blepharospasm, writer's cramp)
- **dystonia-plus syndromes:** dopa-responsive dystonia, myoclonus-dystonia
- **secondary dystonia:** thalamotomy, stroke, CNS tumour, demyelination, PNS injury, drugs/toxins (L-dopa, neuroleptics, anticonvulsants, Mn, CO, cyanide, methanol)
- **heredodegenerative dystonias:** Parkinsonian disorders, Wilson's disease, Huntington's disease

**4. Myoclonus**
- **physiologic myoclonus:** hiccups, nocturnal myoclonus
- **essential myoclonus:** myoclonus-dystonia with minimal or no occurrence of dystonia
- **epileptic myoclonus**
- **symptomatic myoclonus**
- **degenerative disorders:** Wilson's disease, Huntington's disease, corticobasal degeneration
- **infectious disorders:** CJD, viral encephalitis, AIDS-dementia complex
- **metabolic disorders:** drug intoxication/withdrawal, hypoglycemia, hyponatremia, hyperglycemic hyperosmolar syndrome, hepatic encephalopathy, uremia, hypoxia
- **focal brain damage:** head injury, stroke, mass

**Palatal myoclonus** can result from lesion to the Dentato-Rubro-Olivary tract and is associated with an audible clicking and tremor of other facial muscles

# Parkinson's Disease

## Etiology
- sporadic: combination of oxidative stress to dopaminergic neurons, environmental toxins (e.g. pesticides), accelerated aging, genetics
- familial (10%): autosomal dominant α-synuclein or LRRK2 mutations, autosomal recessive parkin, PINK1, or DJ-1mutation (juvenile onset)
- MPTP (neurotoxin)

## Epidemiology
- prevalence of 0.3% in industrialized countries, but rises with increased age
- second most common neurodegenerative disorder, after Alzheimer's disease
- mean age of onset is 60 yr

## Associated Factors
- risk: family history, male, head injury, rural living, exposure to certain neurotoxins
- protective: coffee drinking, smoking, NSAID use, estrogen replacement in post-menopausal women

## Pathophysiology
- loss of dopaminergic neurons in pars compacta of substantia nigra → decreased dopamine in striatum → 1. disinhibition of the indirect pathway, and 2. decreased activation of the direct pathway → increased inhibition of cortical motor areas
- α-synucleinopathy: α-synuclein accumulates in Lewy bodies and causes neurotoxicity in substantia nigra

## Clinical Features
- diagnosis is based on clinical features:
  1. Negative motor
     - bradykinesia: slow, small amplitude movements, fatigue from rapid alternating movements, difficulty initiating movement
  2. Positive motor
     - resting tremor: typically 4-6 Hz "pill-rolling" tremor, especially in hands
     - rigidity: lead-pipe rigidity with cogwheeling due to superimposed tremor
  3. Asymmetric onset of tremor, rigidity, bradykinesia
  4. Progressive course
  - other signs and symptoms of Parkinson's disease include:
    - related findings: masked facies, hypophonia, aprosody (monotonous speech), dysarthria, micrographia, shuffling gait with decreased arm swing
    - freezing of gait: occurs with walking triggered by initiating stride or barriers/destinations, lasting seconds
    - postural instability: late finding presenting as falls
    - cognition: bradyphrenia (slow to think/respond), dementia (late finding)
    - behavioural: decreased spontaneous speech, depression, sleep disturbances, anxiety
    - autonomic: constipation, urinary retention, sexual dysfunction, orthostatic hypotension, clinostatic hypertension

## Treatment
- **pharmacologic**
  - mainstay of treatment: levodopa/carbidopa (Sinemet®) or levodopa/benserazide (Prolopa®)
  - Levodopa is a dopamine precursor; carbidopa and benserazide decrease peripheral metabolism of levodopa, decreasing side effects and increasing half-life of levodopa
    - levodopa-related fluctuation: delayed onset of response (affected by mealtime), end-of-dose deterioration ("wearing-off"), random oscillations of on-off symptoms
    - major adverse effect of levodopa is dyskinesia
  - treatment of early PD: dopamine agonists, amantadine, MAOI
  - adjuncts: dopamine agonists, MAOI, anticholinergics (especially if prominent tremors), catechol-O-methyltransferase inhibitors
- **surgical**
  - thalamotomy
  - pallidotomy
  - deep brain stimulation (thalamic, pallidal, subthalamic)
- **psychiatric**
  - SSRIs first line
  - TCAs (beware fall risk, cognitive impairment, and worsening symptoms of Parkinson's disease)

**Key Parkinsonian Features**

**TRAP**
**T**remor (resting)
**R**igidity
**A**kinesia/bradykinesia
**P**ostural instability

**2015 MDS Clinical Diagnostic Criteria for PD**
**"Clinically Established PD" requires:**
- Cardinal Parkinsonism Manifestations: Bradykinesia with either rest tremor or rigidity
- 2 or more supportive criteria (clear and dramatic beneficial response to dopaminergic therapy, levodopa-induced dyskinesia, rest tremor of a limb, olfactory loss/cardiac sympathetic denervation on MIBG scintigraphy)
- No absolute exclusion criteria and no red flags (see full diagnostic criteria - Mov Disord 2015;30:1591-601)

**Consider an Alternative Diagnosis if Atypical Parkinsonism**
- Poor response to levodopa
- Abrupt onset of symptoms
- Rapid progression
- Early falls
- Early autonomic dysfunction
- Symmetric symptoms at onset
- Early age of onset (<50 yr)
- Early cognitive impairment
- FHx of psychiatric/dementing disorders
- Recent diagnosis of psychiatric disease
- History of encephalitis
- Unusual toxin exposure
- Extensive travel history

# Other Parkinsonian Disorders

- **NCD with Lewy bodies** (see *Behavioural Neurology*, N20)
- **progressive supranuclear palsy:** tauopathy with limited vertical gaze (downgaze more specific) that can be overcome by the oculocephalic reflex, early falls, wide-based unsteady gait, axial rigidity; and akinesia, dysarthia, and dysphagia
- **corticobasal syndrome:** tauopathy with varied presentations but classically presenting with unilateral parkinsonism, dystonia/myoclonus, and apraxia ± "alien limbs" phenomenon; ± progressive non-fluent aphasia

**Dopamine Agonist Therapy in Early Parkinson's Disease**
Cochrane DB Syst Rev 2009;2:CD006564
**Study**: Meta-analysis of trials of dopamine agonists in early Parkinson's disease.
**Results**: Twenty-nine trials were included (n=5247). Dopamine agonists were found to have decreased motor side effects (dyskinesia [OR 0.51], dystonia [OR 0.64], motor fluctuations [OR 0.75]), but provided poorer symptom control compared to levodopa. Also, other side effects were increased (constipation [OR 1.59], hallucinations [OR 1.69], dizziness [OR 1.45]).
**Conclusion**: Dopamine agonists have fewer motor side effects than levodopa, but provide worse symptom control and increased rate of other side effects.

- **multiple system atrophy:** synucleinopathy presenting as either cerebellar predominant (MSA-C, previously olivopontocerebellar atrophy) or parkinsonism predominant (MSA-P, previously nigrostriatal degeneration); both are associated with early autonomic dysfunction (previously Shy-Drager syndrome)
- **vascular parkinsonism:** multi-infarct presentation with gait instability and lower body parkinsonism; less likely associated with tremor

# Huntington's Disease

### Etiology and Pathogenesis
- genetics: autosomal dominant CAG repeats (with anticipation) in huntingtin (HTT) gene on chromosome 4, which leads to accumulation of defective protein in neurons
- pathology: global cerebral atrophy, especially affecting the striatum, leading to increased activity of the direct pathway, and decreased activity of the indirect pathway

### Epidemiology
- North American prevalence 4-8/100,000
- mean age of onset 35-44 yr, but varies with degree of anticipation from 5-70 yr

### Clinical Features
- typical progression: insidious onset with clumsiness, fidgetiness, and irritability, progressing over 15 yr to major NCD, psychosis, and chorea
  - major NCD: progressive memory impairment and loss of intellectual capacity
  - chorea: begins as movement of eyebrows and forehead, shrugging of shoulders, and parakinesia (pseudo-purposeful movement to mask involuntary limb jerking)
  - progresses to dance-like or ballism, and in late stage is replaced by dystonia and rigidity
  - mood changes: irritability, depression, anhedonia, impulsivity, bouts of violence
- Juvenile-onset HD (Westphal variant) characterized by Parkinsonism, dystonia, rigidity, seizures

### Investigations
- MRI
  - enlarged ventricles, atrophy of cerebral cortex, and caudate nucleus
- genetic testing
  - expansion of the cytosine-adenine-guanine (CAG) trinucleotide repeats in the HTT gene
  - CAG repeats (>28) on chromosome 4p16.3 that encodes the protein huntingtin

### Treatment
- no disease-altering treatment
- psychiatric symptoms: antidepressants and antipsychotics
- chorea: neuroleptics and benzodiazepines
- dystonia: botulinum toxin

# Dystonia

### Epidemiology
- 3rd most common movement disorder after Parkinson's disease and essential tremor

### Clinical Features
- sustained or intermittent twitching movements caused by co-contraction of agonist and antagonist muscles
- symptoms exacerbated by fatigue, stress, and emotions; relieved by sleep or specific tactile/proprioceptive stimuli ('geste antagoniste', e.g. place hand on face for cervical dystonia)
- more likely to be progressive and generalized if younger onset or leg dystonia

### Treatment
- local medical: botulinum toxin
- systemic medical: anticholinergics (benztropine), muscle relaxants (baclofen), or benzodiazepines, dopamine depletors (tetrabenazine); dopamine for dopa-responsive dystonia
- surgical: surgical denervation of affected muscle, stereotactic thalamotomy (unilateral dystonia), posteroventral pallidotomy, or DBS

# Tic Disorders

### Definition
- a tic is a sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization
- common criteria
  - tics may wax and wane in frequency but have persisted for an extended period of time
  - onset is <18 yr
  - disturbance is not attributable to the physiological effects of a substance or another medical condition

### Clinical Classification
- **Tourette's Syndrome:** multiple motor and ≥1 vocal tics that have persisted for >1 yr since onset
- **persistent (chronic) motor or vocal tic disorder:** single or multiple motor or vocal tics (but not both motor and vocal) that have persisted for >1 yr since onset

- **provisional tic disorder:** single or multiple motor and/or vocal tics present for <1 yr since first tic onset
- **other specified or unspecified tic disorder:** symptoms characteristic of a tic disorder but do not meet full criteria
- **secondary tic disorders:** encephalitis, CJD, Sydenham's chorea, head trauma, drugs, mental retardation syndromes

### Tic Types
- simple tics: short duration (msec)
- complex tics: longer (seconds), more purposeful and often include a combination of simple tics
- motor tics
  - simple: blinking, head jerking, shoulder shrugging, extension of the extremities
  - dystonic: bruxism (grinding teeth), abdominal tension, sustained mouth opening
  - complex: copropraxia (obscene gestures), echopraxia (imitate gestures), throwing, touching
- vocal tics
  - simple: blowing, coughing, grunting, throat clearing
  - complex: coprolalia (shout obscenities), echolalia (repeat others' phrases), palilalia (repeat own phrases)

### Treatment
- dopamine blockers, dopamine depletors (tetrabenazine), clonidine, clonazepam, or DBS

## Tourette's Syndrome (Gilles de la Tourette Syndrome)

### Definition According to DSM V
1. Presence of both multiple motor and one or more vocal tics at some point during the illness, although not necessarily concurrently
2. Tics may wax and wane in frequency but have persisted >1 yr since first tic onset (with no tic-free periods >3 mo)
3. Onset is <18 yr
4. Not due to effect of a substance or another medical condition

### Epidemiology
- estimated prevalence among adolescents 3-8 per 1000 school-age children; M:F = 2:1-4:1

### Signs and Symptoms
- tics: wide variety that wax and wane in type and severity; can be voluntarily suppressed for some time but are preceded by unpleasant sensation that is relieved once tic is carried out
  - can be worsened by anxiety, excitement, and exhaustion; improved by calm, focused activities
- psychiatric: compulsive behaviour (associated with OCD and ADHD), hyperactive behaviour, 'rages', sleep-wake disturbances, or learning disabilities

### Treatment
- same as tics (dopamine blockers, dopamine depletors, clonidine, clonazepam, DBS)

### Prognosis
- typically begins between ages 4-6
- peak severity occurs between ages 10-12, with a decline in severity during adolescence (50% are tic-free by age 18)
- tic symptoms, however, can manifest similarly in all age groups and across the lifespan

# Cerebellar Disorders

### Clinico-Anatomic Correlations
- **vermis:** trunk/gait ataxia
- **cerebellar lobe (i.e. lateral):** rebound phenomenon, scanning dysarthria, dysdiadochokinesia, dysmetria, nystagmus

### Symptoms and Signs of Cerebellar Dysfunction
- nystagmus: observe during extraocular movement testing (most common is gaze-evoked nystagmus)
- dysarthria (ataxic): abnormal modulation of speech velocity and volume – elicit scanning/telegraphic/slurred speech on spontaneous speech
- ataxia: broad-based, uncoordinated, lurching gait
- dysmetria: irregular placement during voluntary movement of limb or eye
- dysdiadochokinesia: impairment of rapid alternating movements (e.g. pronation-supination task)
- postural instability: truncal ataxia on sitting, titubation (rhythmic rocking of trunk and head), difficulty with tandem and broad-based gait
- intention tremor: typically orthogonal to intended movement, and increases as target is approached
- hypotonia: decreased resistance to passive muscular extension (occurs shortly after injury to lateral cerebellum)
- pendular patellar reflex: knee reflex causes pendular motion of leg (occurs after injury to cerebellar hemispheres), pendular reflexes at triceps
- rebound phenomenon: overcorrection after displacement of a limb
- hypermetric saccades

# Wernicke-Korsakoff Syndrome

- see Psychiatry, PS27
- note that alcohol can also cause a cerebellar ataxia separate from thiamine deficiency; this ataxia can be due to cerebellar atrophy or alcohol polyneuropathy

# Cerebellar Ataxias

### Congenital Ataxias
- early onset non-progressive ataxias associated with various syndromes as well as developmental abnormalities (e.g. Arnold-Chiari malformation, Dandy-Walker cysts)

### Hereditary Ataxias
- **autosomal recessive:** Friedrich's ataxia, ataxia with oculomotor apraxia, ataxia telangiectasia, vitamin E deficiency
  - Friedrich's ataxia: prevalence 2/100,000; typical onset between 8-15 yr
    - signs: gait and limb ataxia, weakness, areflexia, extensor plantar reflex, impaired proprioception and vibration, dysarthria
    - death in 10-20 yr from cardiomyopathy or kyphoscoliotic pulmonary restriction
- **autosomal dominant:** most commonly spinocerebellar ataxias (SCAs); 30+ types, most commonly due to CAG repeats
  - signs: ataxia and dysarthria, chorea, polyneuropathy, pyramidal and/or extrapyramidal features, dementia

### Acquired Ataxias
- neurodegeneration: e.g. multiple system atrophy
- systemic: alcohol, celiac sprue, hypothyroidism, Wilson's, thiamine deficiency, vitamin E deficiency
- toxins: carbon monoxide, heavy metals, lithium, anticonvulsants, solvents
- vascular: infarct, bleed, basilar migraine
- autoimmune: MS, Miller-Fischer (GBS)

# Vertigo

- see Otolaryngology, OT12

# Motor Neuron Disease

## Amyotrophic Lateral Sclerosis (Lou Gehrig's Disease)

### Definition
- progressive neurodegenerative disease that causes UMN and LMN symptoms and is ultimately fatal

### Etiology
- idiopathic (most), genetic (5-10% familial, especially SOD1 mutation, other: C9orf72, TARDBP)

### Pathology
- disorder of anterior horn cells of spinal cord, cranial nerve nuclei, and corticospinal tract

### Epidemiology
- 5/100,000; incidence increases with age

### Clinical Features
- limb motor symptoms: segmental and asymmetrical UMN and LMN symptoms
- bulbar findings: dysarthria (flaccid or spastic), dysphagia, tongue atrophy and fasciculations, facial weakness and atrophy
- pseudobulbar affect, frontotemporal dementia (up to 10%)
- sparing of sensation, ocular muscles, bowel, bladder, sphincters

### Investigations
- EMG: chronic denervation and reinnervation, fasciculations
- NCS: to rule out peripheral neuropathy (i.e. multifocal motor neuropathy with conduction block)
- CT/MRI: to rule out cord disease/compression

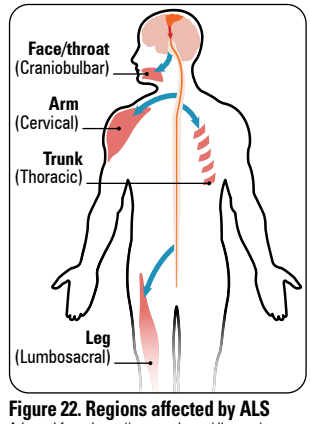



**Figure 22. Regions affected by ALS**
Adapted from: https://www.mda.org/disease/amyotrophic-lateral-sclerosis/signs-and-symptoms and labels: ALS and Other Motor Neuron Diseases (2017) Lecture by Dr. Aaron Izenberg

The only interventions shown to extend survival in ALS are riluzole and use of BiPAP. Edavarone in early ALS can decrease functional decline

**Red Flags Inconsistent with ALS**
Sensory Sx, predominant pain, bowel or bladder incontinence, cognitive impairment, ocular muscle weakness

### Treatment
- riluzole (modestly slows disease progression)
- symptomatic relief
  - spasticity/cramping: baclofen, tizanidine (Zanaflex®), regular exercise, and physical therapy
  - sialorrhea: TCA (i.e. amitriptyline), sublingual atropine drops, parotid/submandibular Botox® (rare)
  - pseudobulbar affect: dextromethorphan/quinidine, TCA, SSRI
- edaravone is FDA and Health Canada approved; reduces functional decline by 33% in early stage ALS
- non-pharmacologic: high caloric diet, ventilatory support (especially BiPAP), early nutritional support (i.e. percutaneous endoscopic gastrostomy tube), rehabilitation (PT, OT, SLP), psychosocial support

### Prognosis
- median survival 3 yr; death due to respiratory failure

**Denervation on EMG**
Fibrillations, positive sharp waves, complex repetitive discharges

**Reinnervation on EMG**
Increased amplitude and duration of motor units

## Other Motor Neuron Diseases

- degenerative
  - **progressive muscular atrophy** (progressive bulbar palsy): only LMN symptoms with asymmetric weakness, later onset than ALS; 5-10% of patients in ALS centres
  - **primary lateral sclerosis** (progressive pseudobulbar palsy): UMN symptoms, later onset, not fatal, variable disability; 5-10% of patients in ALS centres
  - **spinal muscular atrophy**: pediatric disease with symmetric LMN symptoms
- infectious
  - post-polio syndrome
  - West Nile infection: residual asymmetric muscle weakness, atrophy

## Peripheral Neuropathies

### Diagnostic Approach to Peripheral Neuropathies
1. Differentiate: motor vs. sensory vs. autonomic vs. mixed
2. Pattern of deficit: symmetry; focal vs. diffuse; upper vs. lower limb; cranial nerve involvement
3. Temporal pattern: acute vs. chronic; relapsing/remitting vs. constant vs. progressive
4. History: PMH, detailed FHx, exposures (e.g. insects, toxins, sexual, travel), systemic symptoms
5. Detailed peripheral neuro exam: LMN findings, differentiate between root and peripheral nerves, cranial nerves, respiratory status

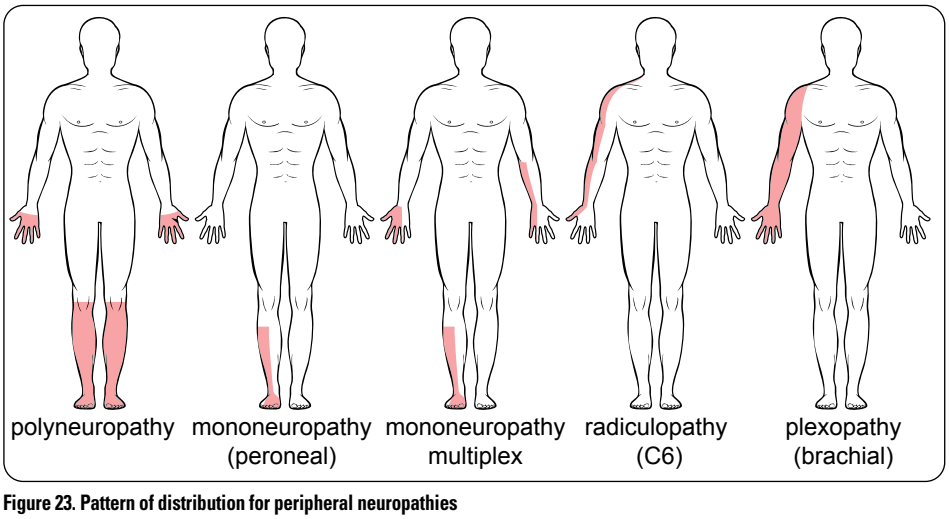



**Figure 23. Pattern of distribution for peripheral neuropathies**

**Diabetic Neuropathies**
- Peripheral neuropathy: pain or loss of sensation in a glove and stocking distribution (hands and feet affected before arms and legs)
- Autonomic: anhidrosis, orthostatic hypotension, impotence, gastroparesis, bowel and bladder dysfunction
- Mononeuropathy multiplex: nerve infarct or compression
- Cranial neuropathy: CN III (pupil sparing) > IV > VI
- Lumbosacral plexopathy

### Classification
- **monoradiculopathy**: dermatomal deficit due to single nerve root lesion
  - due to disc herniation or root compression causing radicular pain
  - little tactile anesthesia, as dermatomes overlap
- **polyradiculopathy**: multiple dermatome deficits due to multiple nerve root lesions (e.g. one type is cauda equina syndrome (lumbosacral roots))
- **plexopathy**: deficit matching distribution of a nerve plexus
  - **brachial plexopathy**
    - upper (C5-C7): LMN Sx of shoulder and upper arm muscles (Erb's palsy)
    - lower (C8-T1): LMN Sx and sensory Sx of forearm and hand (Klumpke's palsy)
    - DDx: trauma, idiopathic neuritis, tumour infiltration, radiation, thoracic outlet syndrome (i.e. cervical rib)
  - **lumbosacral plexopathy** (rare, especially unilateral)
    - DDx: idiopathic neuritis, infarction (i.e. DM), compression

**Tinel's Sign**
Tap lightly over the median nerve at the wrist; the patient's symptoms of carpal tunnel will be elicited in a positive test

**Phalen's Test**
Hold both wrists in forced flexion (with the dorsal surfaces of the hands pressed against each other) for 30-60 s; test is positive if symptoms of carpal tunnel are elicited

**DDx of Demyelinating Neuropathy**
GBS, CIDP, paraproteinemia, diphtheria, amiodarone, Charcot-Marie-Tooth, storage diseases, pressure palsy predisposition, paraneoplastic

- **mononeuropathy**: single nerve deficit
  - **carpal tunnel syndrome** (most common): compression of median nerve at wrist
    - symptoms: wrist pain, paresthesia first 3 and ½ digits, ± radiation to elbow, worse at night
    - signs: Tinel's sign, Phalen's test, thenar muscle wasting, sensory deficit
    - EMG/NCS: slowing at wrist (both motor and sensory)
    - etiology: entrapment, pregnancy, DM, gammopathy, rheumatoid arthritis, thyroid disease
  - **Bell's palsy** (most common cranial neuropathy): see Otolaryngology, OT22
  - **Entrapment/compression**: ulnar (compression at elbow), median (at pronator teres), radial (at spiral groove of humerus), obturator (from childbirth), peroneal (due to crossing legs or surgical positioning), posterior tibial (tarsal canal)
- **mononeuropathy multiplex**: deficit affecting multiple discrete nerves (asymmetric)
  - must rule out vasculitis or collagen vascular disease; consider MMN (multifocal motor neuropathy) or MADSAM (multifocal acquired demyelinating sensory and motor neuropathy)
- **polyneuropathy**: symmetrical distal stocking-glove pattern
  - symmetrical distal sensorimotor deficit affecting longest fibres first (stocking-glove distribution), hypotonia; progression of dysesthesia earlier and weakness later
  - etiology: DM (most common), renal disease, substances, toxins, genetics, SLE, HIV, leprosy, alcohol, B12 deficiency, uremia
  - **chronic inflammatory demyelinating polyneuropathy (CIDP)**
    - chronic relapsing sensorimotor polyneuropathy with increased protein in CSF and demyelination (shown on EMG/NCS)
    - course is fluctuating, in contrast with the acute onset of GBS
    - treatment: first-line is prednisone; alternatives are plasmapheresis, IVIG, and azathioprine



Axonal neuropathies have decreased amplitude on NCS; demyelinating neuropathies have decreased velocity on NCS



Ototoxic drugs (e.g. aminoglycosides) should not be given to diabetics
Sensory neuropathy of the feet prevents them from adequately compensating for loss of vestibular function



IVIG and plasmapheresis lead to more rapid improvement, less intensive care, and less ventilation, but do not change mortality or relapse rate

**Table 18. Differential Diagnosis of Symmetric Polyneuropathy**

| | Etiology | Mechanism | Course | Modalities | Investigations |
|---|---|---|---|---|---|
| **Vascular** | PAN | Ischemic | Chronic | S/M | See Rheumatology, RH20 |
| | SLE | Ischemic | Chronic | S/M | See Rheumatology, RH11 |
| | RA | Ischemic | Chronic | S/M | See Rheumatology, RH8 |
| **Infectious** | HIV | Axonal/demyelination | Chronic | S/A | HIV serology |
| | Leprosy | Infiltrative | Acute | S/A | Leprosy serology<br>Nerve biopsy |
| | Lyme | Axonal/demyelination | Chronic | M | Lyme serology |
| **Immune** | GBS | Demyelination | Acute | M | LP (↑ protein; no ↑ cells) |
| | CIDP | Demyelination | Chronic | S/M | LP (↑ protein) |
| **Hereditary** | HMSN | Axonal/demyelination | Chronic | S/M | Genetic testing |
| **Neoplastic** | Paraneoplastic | Axonal/demyelination | Chronic | S/M | Paraneoplastic antibodies |
| | Myeloma | Axonal/demyelination | Chronic | S/M | SPEP<br>Skeletal bone survey |
| | Lymphoma | Axonal | Chronic | M | SPEP<br>Bone marrow biopsy |
| | Monoclonal gammopathy | Demyelination | Chronic | S/M | SPEP<br>Bone marrow biopsy |
| **Toxin** | EtOH | Axonal | Sub-acute | S/M | GGT, MCV |
| | Heavy metals (i.e. lead) | Axonal | Sub-acute | S/M | Urine heavy metals |
| | Medications | Axonal | Sub-acute | S/M | Drug levels |
| **Metabolic** | DM | Ischemic/axonal | Chronic | S/A | Fasting glucose, HbA1c, 2 h OGTT |
| | Hypothyroidism | Axonal | Chronic | S/M | TSH, T3, T4 |
| | Renal failure | Axonal | Chronic | S/A | Electrolytes, Cr, BUN |
| **Nutritional** | B12 deficiency | Axonal | Sub-acute | S/M | Vitamin B12 |
| **Other** | Porphyria | Axonal | Sub-acute | M | Urine porphyrins |
| | Amyloid | Axonal | Sub-acute | S | Nerve biopsy |

A = autonomic; CIDP = chronic inflammatory demyelinating polyneuropathy; GGT = gamma-glutamyl transferase; HMSN = hereditary motor sensory neuropathy; M = motor; OGTT = oral glucose tolerance test; PAN = polyarteritis nodosa; RA = rheumatoid arthritis; S = sensory; SLE = systemic lupus erythematosus; SPEP = serum protein electrophoresis



**Evaluation of Distal Symmetric Polyneuropathy: Role of Laboratory and Genetic Testing**
Neurology 2009;72:185-92
**Screening Lab Tests**: Blood glucose, serum B12 with metabolites, serum protein immunofixation electrophoresis.
**Genetic Testing**: Indicated for cryptogenic polyneuropathy exhibiting classic hereditary neuropathy phenotype. Screen for CMT1A duplication/deletion and Cx32 mutations.

### Guillain-Barré Syndrome

- **definition**: acute rapidly evolving demyelinating inflammatory polyradiculoneuropathy that often starts in the distal lower limbs and ascends
- **etiology**
  - autoimmune attack and damage to peripheral nerve myelin
  - sometimes preceded by viral/bacterial infections
- **signs and symptoms**
  - sensory: distal and symmetric paresthesias, loss of proprioception and vibration sense, neuropathic pain
  - motor: weakness starting distally in legs, areflexia
  - autonomic: blood pressure dysregulation, arrhythmias, bladder dysfunction
- **investigations**
  - CSF: albuminocytologic dissociation (high protein, normal WBC)
  - EMG/NCS: conduction block, differential or focal (motor > sensory) slowing, decreased F-wave, sural sparing
- **treatment**
  - IVIG or plasmapheresis, pain management, monitor vitals and vital capacity
- **prognosis**
  - peak of symptoms at 2-3 wk, resolution at 4-6 wk
  - 5% mortality (higher if require ICU); up to 15% have permanent deficits

GBS is a neurological emergency due to risk of imminent respiratory failure

The most common antecedent infection in GBS is *Campylobacter jejuni*

**Miller-Fischer Variant of GBS – Triad**
- Ophthalmoplegia
- Ataxia
- Areflexia

# Neuromuscular Junction Diseases

## Clinical Approach to Disorders of the Neuromuscular Junction

**Table 19. Common Disorders of the Neuromuscular Junction**

| | Myasthenia Gravis | Lambert-Eaton | Botulism |
|---|---|---|---|
| **Ocular/Bulbar Paresis** | + | – | ++ (early) |
| **Limb Weakness** | + | + | + |
| **Fatigability** | + | + | + |
| **Post-Exercise Enhancement** | – | + | + |
| **Reflexes** | N | ↓ | ↓ |
| **Anticholinergic Sx** | – | + | ++ |
| **Sensory Sx** | – | – | – |
| **Associated Conditions** | Thymoma | Small cell carcinoma | GI S&S |
| **Repetitive EMG Stimulation** | Decremental response | Incremental response | ↑ (rapid stimulation)<br>↓ (slow stimulation) |

**Neuromuscular Junction Disease**
- Diseases of the neuromuscular junction typically feature prominent fatigability
- Fatigability can be tested by holding the arms out or by holding the gaze in the upward position (especially in MG)
- Muscle weakness due to fatigability will improve with rest or ice

# Myasthenia Gravis

### Etiology and Pathophysiology

- progressive autoimmune disorder due to anti-ACh or anti-muscle specific kinase antibodies, resulting in early saturation at the NMJ and inadequate muscle activation with increasing nerve stimulation
- 15% of patients with MG have associated thymic neoplasia, 85% have thymic hyperplasia

### Epidemiology

- bimodal age of onset – 20s (mostly women) and 60s (mostly men)

### Clinical Features

- fatigable, symmetric, or asymmetric weakness without reflex changes, sensory changes, or coordination abnormalities
- ocular (diplopia/ptosis), bulbar (dysarthria/dysphagia), and/or proximal limb weakness
- symptoms may be exacerbated by infection, pregnancy, menses, and various drugs
- respiratory muscle weakness may lead to respiratory failure

### Investigations

- edrophonium (Tensilon®) test - assess for improvement over 2 min following edrophonium injection
- EMG
  - repetitive stimulation → decremental response
  - single fibre electromyography shows increased jitter (80-100% sensitivity)
- spirometry – forced vital capacity may be used to monitor adequacy of respiratory effort over time
- anti-AChR antibody assay (70-80% sensitivity); anti-MuSK antibody may be used if seronegative for anti-AChR antibody
- CT/MRI to screen for thymoma/thymic hyperplasia

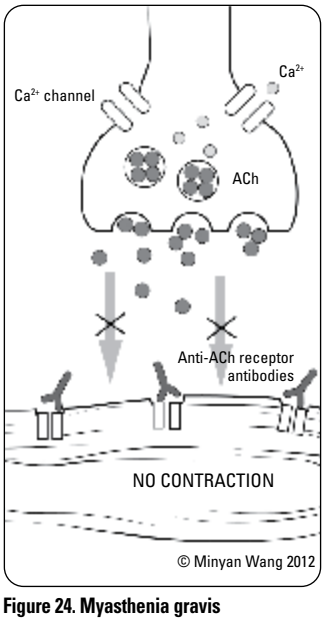



**Figure 24. Myasthenia gravis**

### Treatment
- first line treatment: acetylcholinesterase inhibitors (e.g. pyridostigmine)
- corticosteroids (e.g. prednisone): mainstay of treatment if acetylcholinesterase inhibitors not effective
- immunosuppression (e.g. azathioprine, cyclophosphamide, mycophenolate): can be used as steroid-sparing therapy
- short-term immunomodulation (e.g. IVIG and plasmapheresis): for crisis
- thymectomy: option in non-thymomatous MG; 85% remission rate

### Prognosis
- 30% eventual spontaneous remission
- with treatment, life expectancy is equal to that of a person without MG, but quality of life may vary

Tensilon® is a drug that inhibits acetylcholinesterase. It improves muscle function immediately in myasthenia gravis, but not in a cholinergic crisis.This test is infrequently used; when performed, a crash cart should be nearby as respiratory difficulty and/or bradycardia may occur

## Lambert-Eaton Myasthenic Syndrome

### Etiology and Pathophysiology
- autoimmune disorder due to antibodies against presynaptic voltage-gated calcium channels, causing decreased ACh release at the NMJ
- 50-66% are associated with small cell carcinoma of the lung

### Clinical Features
- weakness of skeletal muscles without sensory or coordination abnormalities, proximal and lower muscles more affected
- reflexes are diminished or absent, but increase after active muscle contraction
- bulbar and ocular muscles affected in 25% (vs. 90% in MG)
- prominent anticholinergic autonomic symptoms (dry mouth > impotence > constipation > blurred vision)

### Investigations
- edrophonium test → no response
- EMG
  - rapid (>10 Hz) repetitive stimulation → incremental response
  - post-exercise facilitation → incremental response with exercise
- screen for malignancy, especially small cell lung cancer

### Treatment
- tumour removal
- ACh modulation
  - increased ACh release (3,4-diaminopyridine)
  - decreased ACh degradation (pyridostigmine)
- immunomodulation - steroids, plasmapheresis, IVIG

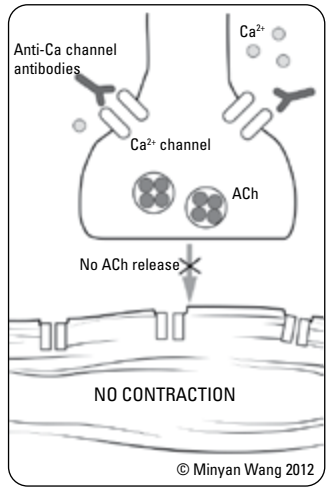



**Figure 25. Lambert-Eaton myasthenic syndrome (LEMS)**

## Botulism

### Etiology and Pathophysiology
- caused by a toxin produced by spores of *Clostridium botulinum* bacteria, which can enter through wounds or by ingestion
- infantile botulism is the most common form and is usually from ingestion of honey or corn syrup

### Clinical Features
- occur 6-48 h after ingestion
- CN paralysis: ptosis, extraocular muscle weakness, dilated poorly reactive pupils, dysarthria, jaw weakness, dysphagia
- autonomic dysfunction: nausea, orthostatic hypotension, constipation (paralytic ileus), bladder distension
- anticholinergic symptoms: dry mouth, constipation, urinary retention
- spreads to trunk and limbs: symmetric weakness with paralysis and absent/decreased deep tendon reflexes
- pattern of paresis often starts with GI symptoms → extraocular muscle weakness → dysphagia → limbs and respiratory involvement; associated with dry mouth
- rarely respiratory distress, potentially advancing to respiratory failure

### Investigations
- blood test for toxin, stool culture
- CT/MRI to rule out stroke, lesion (normal in botulism)

### Treatment
- botulinum anti-toxin – good prognosis with prompt treatment
- supportive therapy as required

# Myopathies

## Clinical Approach to Muscle Diseases

**Table 20. Myopathies**

| | Etiology | Key Clinical Features | Key Investigations |
|---|---|---|---|
| **Inflammatory** | Polymyositis (see Rheumatology , RH15) | Myalgias<br>Pharyngeal involvement | ↑ CK<br>Biopsy: endomysial infiltrates, necrosis |
| | Dermatomyositis (see Rheumatology , RH15) | Myalgias<br>Characteristic rashes<br>Can be paraneoplastic | ↑ CK<br>Biopsy: perifascicular atrophy |
| | Sarcoidosis | See Respirology, R15 | ACE level<br>Biopsy: granulomas |
| | Inclusion body myositis | Weak quadriceps and deep finger flexors | ↑ CK<br>Biopsy: inclusion bodies |
| **Endocrine** | Thyroid (↑ or ↓)<br>Cushing's syndrome<br>Parathyroid (↑ or ↓) | See Endocrinology, E23 | TSH<br>Serum cortisol<br>Calcium panel |
| **Toxic** | Medication | Medication or toxin history | Toxicology screen |
| | Critical illness myopathy | ICU patient<br>Hx steroids and nondepolarizing paralyzing agents<br>Failure to wean from ventilation | Biopsy: selective loss of thick myosin filaments |
| **Infectious** | Parasitic, bacterial, or viral | Myalgias<br>Inflammatory myopathy | ↑ myoglobin |
| **Hereditary Dystrophy** | Duchenne (see Medical Genetics, MG8) | Early onset (Duchenne and Becker) | Dystrophin analysis: absent |
| | Becker | Progressive proximal muscle weakness<br>Calf pseudohypertrophy | Dystrophin analysis: abnormal |
| | Myotonic dystrophy | Distal myopathy<br>Myotonia<br>Genetic anticipation | Genetic testing |
| **Hereditary Metabolic** | McArdle's | Exercise-related myalgias, cramping, and myoglobuminuria | ↑ lactate<br>↑ serum/urinary myoglobin post-exercise |
| **Hereditary Periodic Paralysis** | "Channelopathy" | Episodic weakness<br>Normal between attacks | Normal, ↑ or ↓ K+ |
| **Hereditary Mitochondrial** | MERRF | Myoclonus, generalized seizures, dementia, myopathy | Biopsy: ragged red fibres<br>Increased lactate |
| | MELAS | Pediatric onset, stroke-like symptoms, episodic vomiting, dementia | |
| | Kearns Sayre | Progressive ophthalmoplegia, retinal pigment degeneration, cardiac conduction abnormalities | |

MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF = mitochondrial encephalomyopathy with ragged red fibres
ACE = acetylcholinesterase; CK = creatine kinase



Myopathies are characterized by prominent symmetric proximal weakness and absent sensory changes



**Good Questions to Assess Proximal Weakness**
- Legs: climbing stairs, stand from sit
- Arms: reach above head, wash hair



**Common Medications that Cause Myopathy:** steroids, statins, anti-retrovirals, thyroxine, fibrates, cyclosporine, ipecac
**Common Drugs that Cause Myopathy:** ethanol, cocaine, heroin

# Myotonic Dystrophy

### Etiology and Pathophysiology
- unstable trinucleotide (CTG) repeat in myotonic dystrophy kinase gene (protein kinase) at 19q13.3, number of repeats correlates with severity of symptoms, autosomal dominant

### Epidemiology
- most common adult muscular dystrophy, prevalence 3-5/100,000

### Clinical Features
- appearance: ptosis, bifacial weakness, frontal baldness (including women), triangular face giving a drooping/dull appearance
- physical exam
  - distribution of weakness: distal weaker than proximal (in contrast to other myopathies), steppage gait
  - myotonia: delayed relaxation of muscles after exertion (elicit by tapping on thenar muscles with hammer)
  - cardiac: 90% have conduction defects (1° heart block; atrial arrhythmias)
  - respiratory: hypoventilation 2° to muscle weakness
  - ocular: subcapsular cataracts, retinal degeneration, decreased intraocular pressure
  - other: DM, infertility, testicular atrophy
  - EMG: subclinical myotonia – long runs with declining frequency and amplitude

### Treatment
- management of myotonia: phenytoin

### Prognosis
- no cure, progressive, death usually around 50 yr

# Pain Syndromes

## Approach to Pain Syndromes

### Definitions
- **nociceptive pain**: pain arising from normal activation of peripheral nociceptors
- **neuropathic pain**: pain arising from direct injury to neural tissue, bypassing nociceptive pathways
- **spontaneous pain**: unprovoked burning, shooting, or lancinating pain
- **paresthesia**: spontaneous abnormal non-painful sensation (e.g. tingling)
- **dysesthesia**: evoked pain with inappropriate quality or excessive quantity
- **allodynia**: a dysesthetic response to a non-noxious stimulus
- **hyperalgesia**: an exaggerated pain response to a noxious stimulus

### Non-Pharmacological Management
- physical (PT, acupuncture, chiropractic manipulation, massage)
- psychoeducational (CBT, family therapy, education, psychotherapy)

### Medical Pain Control
- combination multi-modal therapy is important
- primary analgesics: acetaminophen, NSAIDs (often used for soft tissue injuries, strains, sprains, headaches, and arthritis), opiates
- adjuvants: antidepressants (TCAs, SSRIs), anticonvulsants (gabapentin, carbamazepine, pregabalin), baclofen, sympatholytics (phenoxybenzamine), α2-adrenergic agonists (clonidine)

### Surgical Pain Control
- peripheral ablation: nerve blocks, facet joint denervation
- direct delivery: implantable morphine pump
- central ablation: stereotactic thalamotomy, spinal tractotomy, or dorsal root entry lesion
- DBS or dorsal column stimulation

## Neuropathic Pain

### Definition
- pain resulting from a disturbance of the CNS or PNS

### Epidemiology
- affects up to 6% of people (2 million Canadians)



- Pinprick sensation mediated by Aδ fibres
- Pain due to tissue damage is mediated by C fibres



**WHO Pain Ladder**
- **Mild Pain**: Non-opioid (acetaminophen and/or NSAID) ± adjuvant
- **Moderate Pain**: Opioid for mild to moderate pain (codeine/oxycodone) + non-opioid ± adjuvant
- **Severe Pain**: Opioid for moderate to severe pain (morphine/hydromorphone) + non-opioid ± adjuvant



Axonal regeneration is directed by intact nerve sheaths; if the nerve sheath is damaged, axons grow without direction, become tangled, and form a neuroma. This can result in ectopic electrical impulses and neuropathic pain

### Symptoms and Signs
- hyperalgesia, allodynia
- subjectively described as burning, heat/cold, pricking, electric shock, perception of swelling, numbness
- can be spontaneous or stimulus evoked, distribution may not fall along classical neuro-anatomical lines
- associated issues: sleep difficulty, anxiety/stress/mood alteration

### Causes of Neuropathic Pain
- **sympathetic**: CRPS
- **non-sympathetic**: damage to peripheral nerves
  - systemic disease: DM, thyroid disease, renal disease, rheumatoid arthritis, multiple sclerosis
  - nutritional/toxicity: alcoholism, pernicious anemia, chemotherapy
  - infectious: post-herpetic, HIV
  - trauma/compression: nerve entrapment, trigeminal neuralgia, post-surgical, nerve injury, cervical/lumbar radiculopathy, plexopathy
- **central**: abnormal CNS activity
  - phantom limb, post spinal cord injury, post stroke, MS

### Treatment
- identify/treat underlying cause
- **pharmacotherapy**
  - stepwise approach (Canadian Pain Society, 2014)
    - 1st line: gabapentinoids, TCA, SNRI
    - 2nd line: tramadol, opioid analgesics
    - 3rd line: cannabinoids
    - 4th line: topical lidocaine (second line for postherpetic neuralgia), methadone, lamotrigine, lacosamide, tapentadol, botulinum toxin
- **common non-pharmacologic therapies**
  - neuropsychiatry: CBT, psychotherapy
  - rehabilitation: physiotherapy
- **surgical therapies**: dorsal column neurostimulator, DBS (thalamus)

## Trigeminal Neuralgia

### Clinical Features
- recurrent episodes of sudden onset, excruciating, unilateral, paroxysmal, shooting "electric" pain in trigeminal root territory (V3>V2>>V1)
- may have normal sensory exam
- pain lasts seconds/minutes over days/weeks; may remit for weeks/months
- triggers: touching face, eating, talking, cold wind, shaving, applying make-up

### Etiology
- classic TN: compression of CN V by tortuous blood vessel (usually superior cerebellar artery)
- 2º TN: cerebellopontine angle tumour (5%), MS (5%)
- idiopathic TN

### Epidemiology
- F>M; usually middle-aged and elderly

### Diagnosis
- clinical diagnosis
- investigate for secondary causes, which are more likely if bilateral TN or associated sensory loss
  - MRI to rule out structural lesion, MS, or vascular lesion

### Treatment
- first line: carbamazepine or oxcarbazepine
- second line: baclofen or lamotrigine
- for medically-refractory classic TN, consider microvascular decompression
- other neurosurgical options for medically-refractory TN: trigeminal ganglion percutaneous technique, gamma knife radiosurgery, invasive percutaneous denervation (radiofrequency/glycerol), percutaneous balloon microcompression, microvascular decompression
- narcotics not generally recommended

## Postherpetic Neuralgia

### Clinical Features
- pain persisting in the region of a cutaneous outbreak of herpes zoster
- constant deep ache or burning, intermittent spontaneous lancinating/jabbing pain, allodynia
- distribution: thoracic, trigeminal, cervical, lumbar, sacral
- associated symptoms: impaired sleep, decreased appetite, decreased libido



**Herpes Zoster of Trigeminal Nerve**
Typically involves V1 (ophthalmic division)
**Hutchinson's Sign**
Tip of nose involvement predicts corneal involvement

### Etiology and Pathogenesis
- destruction of the sensory ganglion neurons (e.g. dorsal root, trigeminal, or geniculate ganglia) secondary to reactivation of herpes zoster infection

### Epidemiology
- incidence in those with zoster increases with age (2% in <60 yr, 19% in >70 yr)
- risk factors: older age, greater acute pain, greater rash severity

### Prevention
- varicella zoster vaccine (Varivax®) in childhood reduces incidence of varicella zoster
- herpes zoster vaccine (Zostavax® or Shingrix®) reduces incidences of shingles, PHN, and other herpetic sequelae
  - Zostavax® is a live vaccine, recommended for patients ≥60 yr old
  - Shingrix® is a recombinant vaccine, recommended for patients ≥50 yr old (more efficacious than Zostavax®)

### Treatment
- medical: TCA (e.g. amitriptyline), anti-convulsants (e.g. pregabalin, gabapentin), analgesia (e.g. opiates, lidocaine patch), intrathecal methylprednisolone, topical capsaicin
  - early treatment of acute herpes zoster with antivirals (longer-acting famciclovir and valacyclovir more effective)
  - treatment of herpes zoster with corticosteroids DOES NOT decrease PHN
- surgical: spinal tractotomy, dorsal root entry zone lesion, DBS of thalamus

## Painful Diabetic Neuropathy

- see Endocrinology, E14

### Approach
- determine if pain is neuropathic or vascular
- more likely neuropathic if pain is present at rest and improves with walking, pain is sharp/tingling, more in feet → calves

### Treatment
- Level A: pregabalin
- Level B: venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, rarely opioids, capsaicin

## Complex Regional Pain Syndromes

### Definition
- regional pain disproportionate to an inciting event (e.g. fracture, stroke), typically lasting 4-6 wk

### Diagnosis
- clinical diagnosis consistent with the Budapest Criteria:
  1. continuing regional pain disproportionate to an inciting event
  2. patient must have symptoms in 3 of the 4 categories, and must have signs in 2 of the 4 categories (a sign must be observed at the time of diagnosis):
     - sensory: hyperesthesia and/or allodynia
     - vasomotor: temperature and/or skin colour asymmetry
     - sudomotor/edema: edema, sweating changes, and/or sweating asymmetry
     - motor/trophic: decreased range of motion, motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, skin, nail)
  3. absence of any other diagnosis that would better explain the signs or symptoms
- bone scintigraphy ≤5 mo of symptom onset may support diagnosis (negative test does not rule it out)
- MRI may help rule out other causes of regional pain if indicated

### Classification
- CRPS type I (reflex sympathetic dystrophy): minor injuries of limb or lesions in remote body areas precede onset of symptoms
- CRPS type II (causalgia): injury of peripheral nerves precedes the onset of symptoms

### Prevention
- early mobilization after injury/infarction

### Treatment
- goal of treatment is to facilitate function
- conservative treatment: education, support groups, PT, OT, smoking cessation
- medical: topical capsaicin; TCA; NSAID; tender point injections with corticosteroid/lidocaine; gabapentin/pregabalin/lamotrigine; calcitonin or bisphosphonates; oral corticosteroids
- surgical: paravertebral sympathetic ganglion blockade
- refer to pain management clinic

# Headache

- see Emergency Medicine, ER23 and Family Medicine, FM32

## Clinical Approach

- **history**
  - pain characteristics: onset, frequency, duration, intensity, location, radiation, other specific features (e.g. worse in AM, worse with bending/coughing/Valsalva)
  - associated symptoms: visual changes, change in mental status, nausea/vomiting, fever, meningismus, photophobia, phonophobia, temporomandibular popping/clicking, jaw claudication, neurological symptoms
  - precipitating/alleviating factors (triggering factors, analgesics), medications (especially nitrates, calcium channel blockers, NSAIDs, anticoagulants), PMHx, FHx
  - red flags (possible indications for CT scan/further investigation): new-onset headache (especially if age <5 or >50), quality worse/different than previous headaches, sudden and severe ('thunderclap'), immunocompromised, fever, focal neurological deficits, trauma
- **physical exam**
  - vitals (including BP and temperature), Jolt accentuation/Kernig's/Brudzinski's, MSK examination of head and neck
  - HEENT: fundi (papilledema, retinal hemorrhages), red eye, temporal artery tenderness, sinus palpation, TMJ
  - full neurological exam (including LOC, orientation, pupils [symmetry], and focal neurological deficits)
  - red flags: papilledema, altered LOC, fever, meningismus, focal neurological deficits, signs of head trauma

## Classification

- primary
  - tension, migraine, cluster, other autonomic cephalgias, short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT)
- secondary
  - cervical OA, TMJ syndrome, SAH, ICH, stroke, venous sinus thrombosis, meningitis/encephalitis, trauma, increased ICP (space-occupying lesion, malignant HTN, or pseudotumour cerebri), temporal arteritis, sinusitis, acute-angle closure glaucoma, pre-eclampsia, post LP, drugs/toxins (e.g. nitroglycerin use and analgesia withdrawal); all can be associated with serious morbidity or mortality

**Table 21. Headaches – Selected Primary Types**

| | Tension-Type | Migraine | Cluster |
|---|---|---|---|
| **Prevalence** | 70% | ~10-20% | <1% |
| **Age of Onset** | 15-40 | 10-30 | 20-40 |
| **Sex Bias** | F>M | F>M | M>F |
| **Family History** | None | +++ | + |
| **Location** | Bilateral frontal<br>Nuchal-occipital | Unilateral > bilateral<br>Fronto-temporal | Retro-orbital |
| **Duration** | Minutes-days | Hours-days | 10 min-2 h |
| **Onset/Course** | Gradual; worse in PM | Gradual; worse in PM | Daily attacks for weeks to months; more common early AM or late PM |
| **Quality** | Band-like; constant | Throbbing | Constant, aching, stabbing |
| **Severity** | Mild-moderate | Moderate-severe | Severe (wakes from sleep) |
| **Triggers/Provoking** | Depression<br>Anxiety<br>Noise<br>Hunger<br>Sleep deprivation | Noise/light<br>Caffeine/alcohol<br>Hunger<br>Stress<br>Sleep deprivation | Light<br>EtOH |
| **Palliating** | Rest | Rest | Walking around |
| **Associated Symptoms** | No vomiting<br>No photophobia | Nausea/vomiting<br>Photo/phonophobia<br>Aura | Red watery eye<br>Nasal congestion or rhinorrhea<br>Unilateral Horner's |
| **Management** | Non-pharmacological<br>Psychological counselling<br>Physical modalities (e.g. heat, massage)<br>Pharmacological<br>Simple analgesics<br>Tricyclic antidepressants | Acute Rx<br>ASA<br>NSAIDs<br>Triptans<br>Ergotamine<br>Prophylaxis<br>TCA<br>Anticonvulsants<br>Propranolol | Acute Rx<br>$O_2$<br>Sumatriptan (nasal or injection)<br>Prophylaxis<br>Verapamil<br>Lithium<br>Methysergide<br>Prednisolone |

**Table 22. Prophylactic Management of Migraine Headaches**

If CT is negative but clinically there is suspicion of SAH or meningitis, perform an LP

**Headache DDx**

**ER VISIT**
**E**ye (acute angle closure glaucoma, sinusitis)
**R**ecurrent/Chronic (migraine, tension, cluster, temporomandibular joint disease, cervical OA)
**V**ascular (SAH, ICH, temporal arteritis)
**I**nfectious (meningitis, encephalitis)
**S**ystemic (anemia, anoxia, CO, pre-eclampsia)
**I**CP (mass/abscess, HTN encephalopathy, pseudotumour cerebri)
**T**r[illegible] (concussion, SDH, epidural [illegible])

**Acute and Preventive Pharmacologic Treatment of Cluster Headache**
Neurology 2010;75:463-73
**Study**: Meta-analysis of prospective, double-blind, RCTs of pharmacologic agents for prevention or treatment of cluster headaches.
**Results**: 27 trials were included. Sumatriptan 6 mg SC, zolmitriptan nasal spray 5-10 mg, and 100% oxygen 6-12 L/min received as per level A recommendation for acute treatment. For prevention, Level B recommendations were given for intranasal civamide 100 µg daily and suboccipital steroid injections.
**Conclusion**: Sumatriptan, zolmitriptan, and mid flow oxygen are effective acute treatments for cluster headaches.

**Antiepileptics in Migraine Prophylaxis: An Updated Cochrane Review**
Cephalalgia 2015;35:51-62
**Purpose**: To review the evidence for anticonvulsants in migraine prophylactics.
**Study**: Systematic meta-analysis of 37 published and 3 unpublished prospective, controlled trials of regular use of anticonvulsants to prevent migraines and/or improve quality of life related to migraines.
**Results**: Sodium valproate and topiramate were associated with a reduction of 4 d and 1 d of headache per month, respectively, and patients taking either drug were more than 2 times as likely to experience greater than 50% reduction in headache frequency, versus placebo. Neither drug was associated with undue rates of adverse events, though higher doses of topiramate were associated with increased adverse events. There is insufficient evidence of efficacy with other antiepileptic drugs, including gabapentin, for migraine prophylaxis.
**Conclusions**: Daily sodium valproate 400 mg and topiramate 50 mg are well tolerated and effective in prophylactic treatment of migraine headache in adults.

| Class | Drug | Evidence | Contraindications | Side Effects |
|---|---|---|---|---|
| **β-blockers** | Propranolol<br>Timolol<br>Metoprolol | A<br>A<br>B | Asthma, DM (mask hypoglycemia)<br>CHF | Fatigue<br>Depression<br>Light-headedness |
| **TCA** | Amitriptyline<br>Nortriptyline | A<br>C | Heart disease, glaucoma<br>Avoid in elderly | Sedation<br>Dry mouth<br>Weight gain<br>Light-headedness |
| **CCBs** | Flunarizine | A | Depression, obesity | Weight gain, depression, PD (rare) |
| | Verapamil | B | Heart disease | Weight gain (4.5-9 kg), constipation |
| **AED** | Valproate | A | Liver, renal, pancreatic disease | Weight gain, tremor, alopecia, teratogenic: neural tube defect |
| | Topiramate + folic acid supplement | A | Renal disease | Paresthesia, weight loss, cognitive: memory loss, difficulty concentrating, renal stone (rare) |

**Table 23. Headaches – Selected Serious but Rare Secondary Types**

| | Meningeal Irritation | Increased ICP | Temporal Arteritis |
|---|---|---|---|
| **Age of Onset** | Any age | Any age | >60 yr |
| **Location** | Generalized | Any location | Temporal |
| **Onset/Course** | Meningitis: hours-days<br>SAH: thunderclap onset | Gradual; worse in AM | Variable |
| **Severity** | Severe | Severe | Variable; can be severe |
| **Provoking** | Head movement | Lying down<br>Valsalva<br>Head low<br>Exertion | Jaw claudication |
| **Associated Symptoms** | Neck stiffness<br>Photophobia<br>Focal deficits (e.g. CN palsies) | N/V<br>Focal neurological symptoms<br>Decreased level of consciousness | Polymyalgia rheumatica<br>Visual loss |
| **Physical Signs** | Kernig's sign<br>Brudzinski's sign<br>Meningismus | Focal neurological symptoms<br>Papilledema | Temporal artery changes:<br>Firm, nodular, incompressible<br>Tender |
| **Management** | CT/MRI with gadolinium, LP, antibiotics for bacterial meningitis | CT/MRI and treatment to reduce pressure<br>See Neurosurgery, NS6 | Prednisone<br>See Rheumatology, RH21 |
| **Etiology** | Meningitis, SAH | Tumour, IIH, malignant HTN | Vasculitis (GCA) |

IIH = idiopathic intracranial HTN

# Migraine Headaches

## Definition (Common Migraine)

- ≥5 attacks fulfilling each of the following criteria
  - 4-72 h duration
  - 2 of the following: unilateral, pulsating, moderate-severe (interferes with daily activity), aggravated by routine physical activity
  - 1 of the following: nausea/vomiting, photophobia/phonophobia/osmophobia

## Epidemiology

- 18% females, 6% males; frequency decreases with age (especially at menopause)

## Etiology and Pathophysiology

- theories of migraine etiology
  - depolarizing wave of "cortical spreading depression" across the cerebral cortex that may cause an aura (e.g. visual symptoms due to wave through occipital cortex) and also activate trigeminal nerve afferent fibres
  - possible association with vasoconstriction/dilation
- significant genetic contribution
- triggers: stress, sleep excess/deprivation, drugs (estrogen, nitroglycerin), hormonal changes, caffeine withdrawal, chocolate, tyramines (e.g. red wine), nitrites (e.g. processed meats)

The oral contraceptive pill is contraindicated with complicated migraine due to risk of stroke

Migraine auras can mimic other causes of transient neurological deficits (e.g. TIAs and seizures)

**"Menstrual Migraine" Subtype**
Migraine headache that is associated with the onset of menstruation – usually 2 d before to 3 d after the onset of menstrual bleeding

If patient presents to ED with severe migraine and N/V – consider treating with IV anti-emetics (chlorpromazine, prochlorperazine)

### Signs and Symptoms

- stages of uncomplicated migraine
  1. Prodrome (hours to days before headache onset)
  2. Aura
  3. Headache
  4. Postdrome
- aura
  - self-resolving symptom of focal cerebral dysfunction lasting <60 min
  - examples: visual disturbance (fortification spectra – zigzags; scintillating scotomata – spots), unilateral paresthesia and numbness or weakness, aphasia
- prodrome/postdrome: appetite change, autonomic symptoms, altered mood, psychomotor agitation/retardation
- classification of migraines
  - common migraine: no aura
  - classic migraine: with aura (headache follows reversible aura within 60 min)
  - complicated migraine: with severe/persistent sensorimotor deficits
    - examples: basilar-type migraine (occipital headache with diplopia, vertigo, ataxia, and altered level of consciousness), hemiplegic/hemisensory migraine, ophthalmoplegic migraine
  - acephalgic migraine (i.e. migraine equivalent): aura without headache

### Treatment

- avoid triggers
- mild to moderate migraine
  - 1st line: NSAIDs (ibuprofen, naproxen)
- moderate to severe migraine
  - triptans (most effective), ergots (dihydroergotamine, dihydroergotamine mesylate [DHE])
- migraine prophylaxis: anticonvulsants (valproate, topiramate, gabapentin), TCA (amitriptyline, nortriptyline), propranolol, calcium channel blocker (verapamil)
- medication overuse (use of triptans/opioids/combination analgesics for ≥10 d/mo, or use of NSAIDs for ≥15 d/mo) can lead to medication-overuse headaches

**Pharmacological Treatments for Acute Migraine**
Pain 2002;97:247-57
**Study**: Meta-analysis of 54 double-blind, placebo-controlled RCTs of pharmacologic treatment of acute migraine of moderate to severe intensity (21,022 patients in total).
**Data Extraction**: Number of patients, dosing regimens, details of study design, and timing or type of rescue medication. Outcomes include headache relief at 1 and 2 h, freedom from pain at 2 h, sustained relief for 24 h, and adverse effects within 24 h.
**Main Results**: Data were available for 9 oral medications, 2 intranasal medications, and subcutaneous sumatriptan. For headache relief at 2 h, all interventions were effective except Cafergot®, with NNTs ranging from 2.0 for sumatriptan 6 mg SC to 5.4 for naratriptan 2.5 mg. The lowest NNT for oral medication was 2.6 for eletriptan 80 mg. For patients pain free at 2 h, the lowest NNT was 2.1 for sumatriptan 6 mg SC, with the lowest NNT for oral medication being 3.1 for rizatriptan 10 mg. For sustained relief over 24 h, NNT ranged from 2.8 for eletriptan 80 mg to 8.3 for rizatriptan 5 mg. Side effects could not be analyzed systematically. There were no drug-to-drug comparisons.
**Conclusion**: Overall, most treatments were effective. Subcutaneous sumatriptan and oral triptans were most effective.

# Sleep Disorders

## Overview of Sleep

### Recommendations

- newborn: 18 h sleep (50% REM), adolescents: 10 h, adults: 7-9 h but most get insufficient amounts
- many older patients have reduced sleep as a consequence of underlying sleep disorders

### Sleep Architecture

- polysomnogram (PSG) measures: EEG, eye movements (electro-oculogram – EOG), EMG, respiratory effort, oxygenation, ECG

**Table 24. Sleep Stage Characteristics**

| | EEG | EOG | Muscle Tone | Other Characteristics |
|---|---|---|---|---|
| **Waking State** | Alpha waves: high frequency (8-12 Hz), low voltage | Rapid, blinking | High | |
| **Stage N1 (~5%)** | Less than 50% Alpha waves (see above), mixed with slow wave activity | Slow, roving eye movements | High, but gradually dropping | Marker for very light quality sleep or sleep disruption |
| **Stage N2 (~50%)** | K complexes (high voltage negative and positive discharges) with sleep spindles (11-16 Hz) | Still | High | |
| **Stage N3 (previously 3 and 4)/Slow Wave/ Delta Sleep (~20%)** | Delta waves: low frequency (<2 Hz), high voltage (>75 μV) | Still | Low | Homeostatic sleep<br>Reduced BP, HR, cardiac output, RR<br>Growth hormone release |
| **Rapid Eye Movement Sleep (~25%)** | Sawtooth waves, mixed frequency, low voltage | Rapid eye movements | Very low | Irregular respiration<br>Arrhythmias, heart rate variation<br>Classical dreaming state |

**Elements of Sleep History**

- Initiation of sleep
- Events prior to bed
- Lights
- Latency (estimated)
- Restless legs
- Hallucinations
- Maintaining sleep
- Number of wakeups per night
- Sleep walking/talking
- Snoring/gasping
- Dreams/nightmares
- Consequences of sleep
- Restorative
- Morning headache
- Falling asleep in inappropriate setting

# Disturbances of Alertness and Sleep

## Coma
- see Neurosurgery, NS35

## Insomnia
- difficulty initiating or maintaining sleep, or waking up earlier than desired (leading to sleep that is chronically non-restorative/poor quality) despite adequate opportunity and circumstances for sleep
- **types**
  - sleep state misperception, psychophysiologic insomnia (learned sleep-preventing associations – i.e. clock watching), fatal familial insomnia (rare prion protein mutation causing autonomic dysfunction), idiopathic (lifelong difficulty)
  - **secondary causes**
    - psychiatric disorders (80% of psychiatric patients): depression and anxiety (see Psychiatry, PS12, PS39)
    - neurologic disorders: neurodegenerative disease, epilepsy, neuromuscular disorders, many others
    - sleep disorders: restless legs syndrome (sleep initiation difficulties), sleep apnea (sleep maintenance difficulties)
    - medical conditions: pregnancy, cardiorespiratory (COPD/heart failure), gastroesophageal reflux disease, pain (arthritis, fibromyalgia, cancer)
    - drugs/toxins: caffeine, alcohol, stimulants, antidepressants, glucocorticoids, sedative withdrawal
- **treatment**
  - sleep log, sleep hygiene, stimulus control, sleep restriction, relaxation response, CBT

**Drug Effects on Wakefulness and Sleep**
- Antihistamines associated with increased sleepiness
- Stimulants increase arousal
- Caffeine (an adenosine antagonist) increases wakefulness
- Benzodiazepines reduce slow wave sleep
- Antidepressants (TCA/MAOI/SSRI) reduce REM, prolong REM latency
- Alcohol may hasten sleep onset but is associated with increased arousals

Avoid sleep medications (especially in elderly patients) due to increased risk of falls, pseudodepression, and memory loss

## Sleep Apnea
- disorder of breathing in sleep associated with sleep disruption and consequent excessive somnolence (or drowsiness)
- **epidemiology**
  - >2-4% of the population
  - correlated with obesity
  - significant morbidity: HTN, stroke, heart failure, sleepiness, mortality (accidents)
- **types**
  - obstructive sleep apnea; etiology: collapse of airway due to low muscle tone in deep and REM sleep
  - central sleep apnea: no effort to breath >10 s, etiology: heart failure, opiates, brainstem pathology, myotonic dystrophy
  - mixed apnea: starts as central, but eventually becomes obstructive
- **diagnosis**: apnea hypopnea index (AHI) or respiratory disturbance index (RDI) ≥5
- **treatment**: conservative measures, dental devices, CPAP (common), surgery (rare), ensure driving safety

## Restless Leg Syndrome (RLS) and Periodic Limb Movement in Sleep (PLMS)
- urge to move accompanied by uncomfortable sensations that begin or worsen with rest, are partially or totally relieved with movement, and are worse in evening/night; these features cannot be accounted for by another medical/behavioural condition
- RLS refers to sensation, PLMS refers to the manifestation
- **epidemiology**: 10% North Americans, 90% of RLS have PLMS, 50% of patients with PLMS have RLS
- **etiology**: central (spasticity), peripheral nervous system (radiculopathy, neuropathy), pregnancy, iron deficiency, alcohol use
- **treatment**
  - underlying contributors (iron and B12 supplementation), dopaminergic agonists (first line), clonazepam (causes tachyphylaxis), opioids (only exceptional circumstances)
  - NOT recommended: levodopa/carbidopa (Sinemet®) which causes augmentation

## Narcolepsy
- **definition/clinical features**: excessive daytime sleepiness (all narcolepsy), cataplexy = loss of muscle tone with emotional stimuli (pathognomonic), sleep paralysis (unable to move upon wakening), hypnagogic hallucinations (vivid dreams or hallucinations at sleep onset)
- **epidemiology**: prevalence 1:2000, onset in adolescence/early adulthood; life-long disorder
- **etiology**: presumed autoimmune attack on orexin/hypocretin system, post head injury, MS, hypothalamic tumours; rarely familial
- **diagnosis**: based on clinical history + multiple sleep latency test findings of short sleep latency <8 min and REM within 15 min of sleep onset on 2/4 naps
- **treatment**
  - sleep hygiene and scheduled brief naps, restricted driving
  - alerting agents: modafinil (non-amphetamine stimulant), stimulant (i.e. methylphenidate)
  - anticataplectic: TCAs, SSRIs, sodium oxybate

### Parasomnias
- **definition/clinical features**: unusual behaviours in sleep with clinical features appropriate to stage of sleep
- **etiology**: in elderly, REM sleep behaviour disorder may be associated with PD; in children, slow wave sleep arousals (sleep walking) may be associated with sleep-disordered breathing
- **diagnosis**: clinical history in children, polysomnography in adults to exclude nocturnal seizures
- **treatment**: behavioural management (safety, adequate sleep), clonazepam for REM sleep behaviour, tonsillectomy if appropriate in children

### Circadian Rhythm
- **definition/clinical features**: abnormalities based on time of day rather than sleep (e.g. jet lag, shift work)
- **diagnosis**: clinical history

# CNS Infections

- see Infectious Diseases, ID15

# Spinal Cord Syndromes

- see Neurosurgery, NS29

# Stroke

## Terminology

- **stroke**: sudden onset of neurological deficits of a vascular etiology with infarction of CNS tissue
  - infarction is permanent tissue injury (confirmed by neuroimaging)
- **TIA**: sudden onset of neurological deficits of a vascular etiology without infarction (i.e. no imaging evidence of stroke)
  - may present with amaurosis fugax (transient monocular painless vision loss)

## Pathophysiology

- two major types: ischemic (~80%) and hemorrhagic (~20%)

**1. Ischemic**
- arterial thrombosis: thrombus formation in artery (local/*in situ*)
  - large vessel: stenosis or occlusion of the internal carotid artery, vertebral, or intracranial arteries
    - mechanism: insufficient blood flow beyond lesion (hemodynamic stroke)
    - underlying processes: atherosclerosis (most common cause), dissection, and vasculitis
  - small vessel/lacunar
    - mechanism: chronic HTN and DM cause vessel wall thickening and decreased luminal diameter
    - affects mainly small penetrating arteries (primarily basal ganglia, internal capsule, and thalamus)
- cardioembolic: blockage of cerebral arterial blood flow due to particles originating from a cardiac source
  - atrial fibrillation (most common), rheumatic valve disease, prosthetic heart valves, recent MI, fibrous and infectious endocarditis
- systemic hypoperfusion (global cerebral ischemia)
  - inadequate blood flow to brain, usually secondary to cardiac pump failure (e.g. cardiac arrest, arrhythmia, or MI)
  - primarily affects watershed areas (between the major cerebral arterial territories)

**2. Hemorrhagic**
- intracerebral hemorrhage
  - mechanisms
    - hypertensive (most common): rupture of small microaneurysms (Charcot-Bouchard aneurysms) causing intraparenchymal hemorrhage; most common sites are putamen, thalamus, cerebellum, and pons
    - other: trauma, amyloid angiopathy (associated with lobar hemorrhage), vascular malformations, vasculitis, drug use (cocaine or amphetamines)
- subarachnoid hemorrhage see Neurosurgery, NS18



**Hypertension Encephalopathy**
Acute severe HTN (typically dBP >130 or sBP >200) can cause hypertensive encephalopathy. Abnormal fundoscopic exam (papilledema, hemorrhages, exudates, cotton-wool spots), focal neurologic symptoms, N/V, visual disturbances, and change in LOC



Consider transfer of acute stroke patient to a designated stroke centre for neuroprotective or thrombolytic therapy if the patient is seen in first few hours



Early seizure activity occurs in 5-25% of patients after ICH



Cerebral venous sinus thrombosis should be considered in the differential diagnosis of stroke and headache. It is an uncommon cause of either, but is associated with high morbidity and mortality. Patients often present with headache alone, but can have seizures, focal neurological deficits, or cranial nerve palsies. This is diagnosed with magnetic resonance venography or cerebral CT venography. Treatment is typically anticoagulation with heparin initially, then warfarin eventually



20-40% of patients with ischemic stroke may develop hemorrhagic transformation within 1 wk after the initial infarction



Blood work should only delay treatment if patient is on anticoagulants, low platelet count suspected, abnormal electrolytes suspected, or any bleeding abnormality suspected

## Stroke Syndromes According to Vascular Territory

- **ACA**: contralateral leg paresis, sensory loss, cognitive deficits (e.g. apathy, confusion, and poor judgment)
- **MCA**: proximal occlusion involves
  1. contralateral weakness and sensory loss of face and arm
  2. cortical sensory loss
  3. may have contralateral homonymous hemianopia or quadrantanopia
  4. if dominant (usually left) hemisphere: aphasia
  5. if non-dominant (usually right) hemisphere: neglect
  6. eye deviation towards the side of the lesion (away from the weak side)
- **PCA**
  1. contralateral hemianopia or quadrantanopia
  2. midbrain findings: CN III and IV palsy/pupillary changes, hemiparesis
  3. thalamic findings: sensory loss, amnesia, decreased LOC
  4. if bilateral: cortical blindness or prosopagnosia
  5. hemiballismus
- **basilar artery**
  - proximal (usually thrombosis): impaired EOM, vertical nystagmus, reactive miosis, hemi- or quadriplegia, dysarthria, locked-in syndrome, coma
  - distal (usually embolic, i.e. top of the basilar syndrome): somnolence, memory and behaviour abnormalities, oculomotor deficit
- **PICA** (lateral medullary or Wallenberg syndrome): ipsilateral ataxia, ipsilateral Horner's, ipsilateral facial sensory loss, contralateral limb impairment of pain and temperature sensation, nystagmus, vertigo, nausea/vomiting, dysphagia, dysarthria, hiccups
- **medial medullary infarct** (anterior spinal artery, which can be associated with anterior cord infarct): contralateral hemiparesis (facial sparing), contralateral impaired proprioception and vibration sensation, ipsilateral tongue weakness
- **lacunar infarcts** (deep hemispheric white matter; involving deep penetrating arteries of MCA, circle of Willis, basilar and vertebral arteries)
- **sensorimotor stroke**: weakness and numbness of the face/arm/leg without other cortical signs (i.e. aphasia, apraxia, visual loss)
  - pure motor hemiparesis (posterior limb of internal capsule): contralateral arm, leg, and face
  - pure sensory loss (ventral thalamic): hemisensory loss
  - ataxic hemiparesis (ventral pons or internal capsule): ipsilateral ataxia and leg paresis
  - dysarthria-clumsy hand syndrome (ventral pons or genu of internal capsule): dysarthria, facial weakness, dysphagia, mild hand weakness, and clumsiness

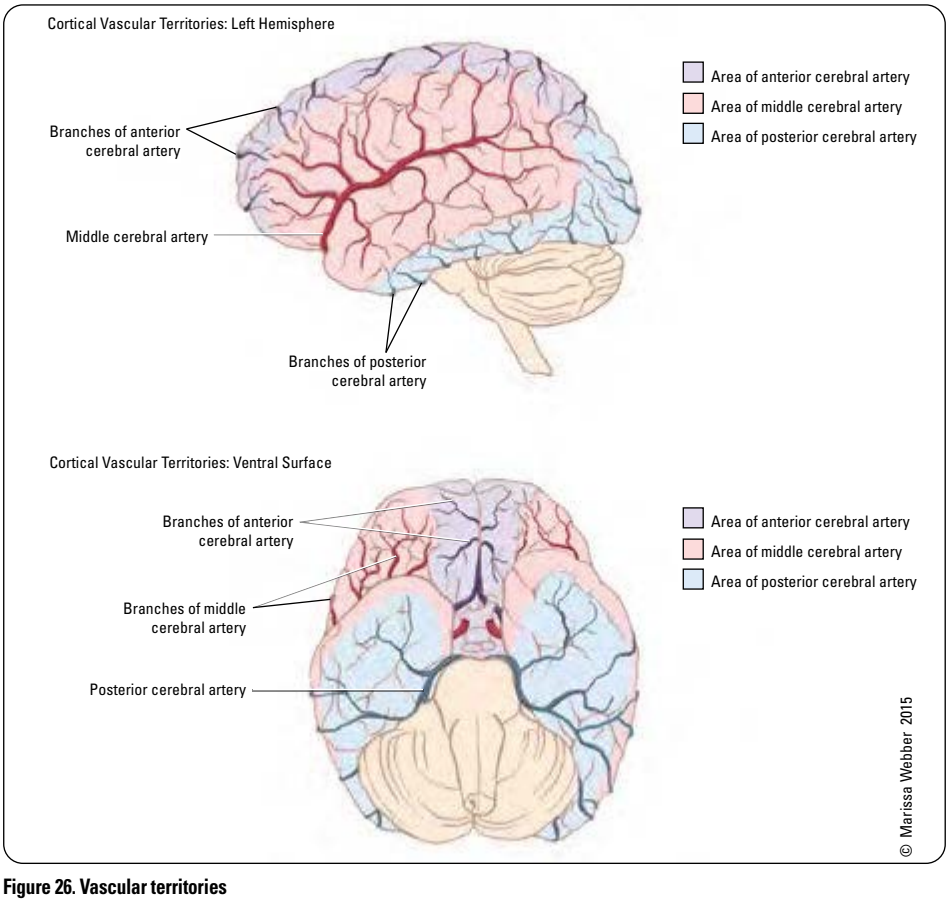



**Figure 26. Vascular territories**

Stroke mimics: drug intoxication, infections, migraines, metabolic, seizures, tumours

Suspect an alternate diagnosis if fever, decreased LOC, fluctuating symptoms, gradual onset, no focal neurological symptoms, and/or positive symptoms

Infarcted area of brain tissue can often appear normal on CT during the first several hours after stroke onset

**Oral Direct Thrombin Inhibitors or Oral Factor Xa Inhibitors for the Treatment of Deep Vein Thrombosis**
Cochrane DB Syst Rev 2015;6:CD010956
**Purpose**: To assess whether direct thrombin inhibitors or factor Xa inhibitors are effective treatment for DVTs.
**Study**: Systematic review search 1950-2015, inclusive. Results included 11 RCTs, 27,945 patients, comparing direct thrombin inhibitors or factor Xa inhibitors to standard treatment (heparin, wafarin, and similar).
**Outcome**: Recurrent DVT or PE.
**Results**: Separate meta-analyses of direct thrombin inhibitors and factor Xa inhibitors showed that each was comparable to standard treatment in terms of DVT recurrence rates. Rates of fatal or non-fatal PE, and all-cause mortality were also not significantly different. Additionally, factor Xa inhibitors had lower rates of bleeding complications than standard treatment (OR 0.57; CI 0.43 to 0.76).
**Conclusions**: New oral treatment options, including direct thrombin inhibitors and factor Xa inhibitors represent reasonable and safe alternatives for acute.

**The National Institute of Health Stroke Scale (NIHSS)** is a standardized clinical examination that determines the severity of an acute stroke; it can also be used to monitor response to treatment over time
The scale uses 11 items that evaluate:
- Level of consciousness
- Visual system
- Motor system
- Sensory system
- Language abilities

Scoring (x/42):
0=no stroke
1-4=mild stroke
5-15=moderate stroke
15-20=moderate to severe stroke
21-42=severe stroke
rtPA is typically considered if score ≥6, but some stroke neurologists will administer rtPA with lower NIH stroke scale scores

# Assessment and Treatment of Ischemic Stroke

## General Assessment

- ABCs, full vital sign monitoring, capillary glucose (Accu-Chek®), urgent CODE STROKE if <4.5 h from symptom onset (for possible thrombolysis)
- LOC (knows age, month; obeys commands), dysarthria, dysnomia (cannot name objects)
- gaze preference, visual fields, facial palsy
- arm drift, leg weakness, ataxia
- sensation to pinprick, extinction/neglect
- **history**
  - onset: time when last known to be awake and symptom free
  - mimics to rule out: seizure/post-ictal, hypoglycemia, migraine, conversion disorder
- **investigations**
  - non-contrast CT head (STAT): to rule out hemorrhage and assess extent of infarct
  - ECG: to rule out atrial fibrillation (cardioembolic cause)
  - carotid dopplers, ECG
  - CBC, electrolytes, creatinine, partial thromboplastin time/international normalized ratio, blood glucose, lipid profile
- **imaging** (i.e. CT ± MR or CT angiography) signs of stroke
  - loss of cortical white-grey differentiation
  - sulcal effacement (i.e. mass effect decreases visualization of sulci)
  - hypodensity of parenchyma
  - insular ribbon sign
  - hyperdense MCA sign

## ACUTE STROKE MANAGEMENT

### 1. Thrombolysis

- rtPA (recombinant tissue plasminogen activator) should be given within 4.5 h of acute ischemic stroke onset provided there are clinical indications and no contraindications to use (see sidebar)

### 2. Anti-Platelet Therapy

- loading dose of antiplatelets at presentation of TIA or stroke if rtPA not received
  - loading dose of ASA: recommended dose 160 mg chewed
  - if patient intolerant to ASA, use another antiplatelet agent (e.g. clopidogrel 300 mg)
- ASA 81 mg daily should be continued indefinitely for secondary prevention

### 3. Acute Anti-Coagulant Therapy

- for patients with TIA or stroke and atrial fibrillation, if rtPA not received:
  - recommend IV heparin (or ensuring international normalized ratio between 2-3 if already anticoagulated on warfarin)
  - may delay initiation of oral anticoagulation depending on size of infarct and presence of petechial/frank hemorrhage

### 4. Intra-Arterial Mechanical Thrombectomy

- early thrombectomy ≤24 h since symptom onset improves outcomes in ischemic stroke with large artery occlusions of the proximal anterior circulation

## Other Acute Management Issues

- avoid hyperglycemia which can increase the infarct size
- lower temperature if febrile (febrile stroke: think septic emboli from endocarditis)
- prevent complications
  - NPO if dysphagia (to be reassessed by SLP)
  - DVT prophylaxis if bed-bound
  - initiate rehabilitation early

## Blood Pressure Control

- do NOT lower the blood pressure unless the HTN is severe
- antihypertensive therapy is withheld for 48-72 h (permissive hypertension) after thromboembolic stroke unless sBP >220 mmHg or dBP >120 mmHg, or in the setting of acute MI, renal failure, aortic dissection (IV labetalol first-line if needed)
- acutely elevated BP is necessary to maintain brain perfusion to the ischemic penumbra
- most patients with an acute cerebral infarct are initially hypertensive but their BP will improve within 1-2 d

## Etiological Diagnosis

- further investigations
  - additional neuroimaging (MRI)
  - vascular imaging: CTA/MRA/carotid dopplers
  - cardiac tests: ECG, Holter monitoring
  - correct etiological diagnosis is critical for appropriate 2º prevention strategies



**Aspect Score: 10-Point Quantitative Score to Assess Ischemic Changes on CT Scan**

- 10/10 is normal and <4/10 signifies high risk of bleed with rtPA
- Subtract 1 point for each of following structures if abnormal within the ischemic hemisphere: caudate, lentiform, insula, internal capsule, MCA 1, 2, 3, 4, 5, 6 regions



If rtPA is given at stroke onset, delay acute antiplatelet/anticoagulation treatment by 24 h



**Absolute Contraindications to rtPA**

**Hx:** improving Sx, minor Sx, seizure at stroke onset, recent major surgery or trauma (within 14 d), recent GI or urinary hemorrhage (within 21 d), recent LP or arterial puncture at noncompressible site, PMHx of ICH, Sx of SAH/pericarditis/MI, pregnancy

**P/E**: sBP ≥185, dBP ≥110, aggressive treatment to decrease BP, uncontrolled serum glucose, thrombocytopenia

**Ix:** hemorrhage or mass on CT, high INR or aPTT



**Factor Xa Inhibitors vs. Vitamin K Antagonists for Preventing Cerebral or Systemic Embolism in Patients with Atrial Fibrillation**

Cochrane DB Syst Rev 2014;8:CD008980

**Purpose**: To review the evidence comparing factor Xa inhibitors with vitamin K antagonists for prevention of embolic events in patients with atrial fibrillation.

**Study**: Inclusive systematic review search for 1950-2013. Results included 10 RCTs, 42,084 patients, follow-up from 12 wk-1.9 yr.

**Outcome**: Stroke (hemorrhagic or ischemic) and non-CNS embolic event

**Results**: Factor Xa inhibitor treatment resulted in significantly fewer embolic events than dose adjusted warfarin treatment (OR 0.81; CI 0.72 to 0.91). There was no significant difference in rate of major bleeds between factor Xa inhibitors and warfarin treatment. Furthermore, factor Xa inhibitors resulted in significantly fewer intracranial bleeds and lower all-cause mortality.

**Conclusions**: Use of factor Xa inhibitor for anti-coagulation in patients with atrial fibrillation offered better protection against embolic events than warfarin. Factor Xa inhibitors also had equal or lower rates of adverse events.



**High-Dose Atorvastatin after Stroke or Transient Ischemic Attack (SPARCL Trial)**

NEJM 2006;355:549-59

**Method**: Multicentre double-blind RCT.

**Population**: 4,731 patients with stroke or TIA within 1-6 mo before study entry, LDL 100-190 mg/dL, no coronary heart disease.

**Intervention**: 80 mg atorvastatin PO OD or placebo.

**Outcome**: First non-fatal or fatal stroke over 5 yr.

**Results**: Patients receiving atorvastatin had a lower rate of stroke (ARI 2.2%, hazard ratio 0.84; p=0.03). There was a 5 yr ARI of 3.5% (p=0.002). There was no significant change in mortality rate, but a small significant increase in the risk of hemorrhagic stroke.

**Conclusions**: High-dose atorvastatin decreases overall incidence of strokes and cardiovascular events in patients with a history of recent stroke or TIA.



**Evaluating for Occult Atrial Fibrillation – CRYSTAL AF Trial**

NEJM 2014:370;2478-86

Patients with a cryptogenic ischemic stroke or TIA and no evidence of atrial fibrillation on ECG and Holter monitoring may benefit from ambulatory cardiac monitoring with subcutaneous implantable loop recorder or external loop recorder for several weeks.

# Primary and Secondary Prevention of Ischemic Stroke

## Anti-Platelet Therapy

- primary prevention
  - no firm evidence of a protective role for antiplatelet agents in low-risk patients without a prior stroke/TIA
- secondary prevention
  - initial choice: ASA
  - if cerebrovascular symptoms while on ASA or if unable to tolerate ASA: Aggrenox® (ESPRIT trial), clopidogrel (CAPRIE trial)

## Carotid Stenosis

- primary prevention (asymptomatic)
  - carotid endarterectomy is controversial: if stenosis >60%, risk of stroke is 2% per yr; carotid endarterectomy reduces the risk of stroke by 1% per yr (but 5% risk of complications)
- secondary prevention (previous stroke/TIA in carotid territory)
  - carotid endarterectomy clearly benefits those with symptomatic severe stenosis (70-99%), and is less beneficial for those with symptomatic moderate stenosis (50-69%) (NASCET trial), see Vascular Surgery, VS9
- according to the CREST trial, endarterectomy and carotid stenting have similar benefits in a composite endpoint of reduction of stroke, MI, and death; however, in the periprocedural period, stenting results in a higher rate of stroke, while endarterectomy results in a higher rate of MI

## Atrial Fibrillation

- primary and secondary prevention with anticoagulation
  - classical risk stratification used $CHADS_2$ score (0-6), but Stroke 2014 guidelines recommend that virtually all patients with atrial fibrillation without contraindication be anticoagulated
    - 0 (low risk, 1.9% annual stroke risk): antiplatelet
    - 1 (intermediate risk, 2.8% annual stroke risk): anticoagulant or antiplatelet – patient specific decision
    - >2 (high risk, 4-18.2% annual stroke risk): anticoagulant
  - anticoagulation therapy
    - warfarin (titrate to international normalized ratio 2-3)
    - dabigatran (110 or 150 mg PO bid), apixaban (2.5 or 5 mg PO bid) or rivaroxaban (15 or 20 mg PO daily) may be alternatives to warfarin, but should be used cautiously; Praxbind® reversal agent for dagibatran if necessary

## Hypertension

- primary prevention
  - targets: BP <140/90 (sBP <120 for high risk without diabetes [SPRINT trial] or <130/80 for diabetics or renal disease)
  - ACEI: ramipril 10 mg PO OD is effective in patients at high risk for cardiovascular disease (HOPE trial)
- secondary prevention
  - ACEI and thiazide diuretics are recommended in patients with previous stroke/TIA (PROGRESS trial)

## Hypercholesterolemia

- primary prevention
  - statins in patients with CAD or at high risk for cardiovascular events, even with normal cholesterol (CARE trial)
- secondary prevention
  - high dose atorvastatin (SPARCL trial) but lower doses may be adequate if patient cannot tolerate high dose

## Diabetes

- ideal management: HbA1c <7%, fasting blood glucose 4-7

## Smoking

- primary prevention: smoking increases risk of stroke in a dose-dependent manner
- secondary prevention: after smoking cessation, the risk of stroke decreases to baseline within 2-5 yr

## Physical Activity

- beneficial effect of regular physical activity has a dose-related response in terms of intensity and duration of activity

## Stroke Rehabilitation

- individualized based on severity and nature of impairment; may require inpatient program and continuation through home care or outpatient services
- multidisciplinary approach includes dysphagia assessment and dietary modifications, communication rehabilitation, cognitive and psychological assessments including screen for depression, therapeutic exercise programs, assessment of ambulation and evaluation of need for assistive devices, splints or braces, vocational rehabilitation

**$CHADS_2$**
Stroke risk stratification for patients with atrial fibrillation
**C**HF (1 point)
**H**TN sBP >160 mmHg/treated HTN (1 point)
**A**ge >75 yr (1 point)
**D**M (1 point)
Prior **S**troke or TIA (2 points)

Carotid endarterectomy needs to be done within 2 wk of the ischemic event for the most benefit

**$ABCD^2$ Score**
To predict/identify individuals at high risk of stroke following TIA
**A**ge: 1 point for age >60 yr
**B**lood pressure (at presentation):
1 point for HTN
(>140/90 mmHg at initial evaluation)
**C**linical features: 2 points for unilateral weakness, 1 point for speech disturbance without weakness
**D**uration of symptoms: 1 point for 10-59 min, 2 points for >60 min
**D**M: 1 point
Stroke risk: 0-3: low risk, 4-5: moderate risk, 6-7: high risk

**Long-Term Results of Stenting vs. Endarterectomy for Carotid-Artery Stenosis**
NEJM 2016; 374:1021-31
**Study**: Patients were randomly assigned to stenting or endarterectomy and assessed every 6 mo for up to 10 yr.
**Population**: 2502 patients at 117 centres with carotid-artery stenosis.
**Outcome**: Primary composite outcome was stroke, myocardial infarction, or death during periprocedural period or subsequent ipsilateral stroke.
**Results**: There was no significant difference in outcomes of either primary composite endpoint (HR 1.10; 95% CI 0.83-1.44) or post-procedural stroke (HR 0.99; 95% CI 0.64-1.52) in patients treated with stenting or endarterectomy. Asymptomatic and symptomatic patients showed no significant between-group differences in either endpoint.
**Conclusions**: The rate of periprocedural stroke, myocardial infarction, death, and subsequent ipsilateral stroke did not differ between carotid-artery stenosis patients treated with stenting or endarterectomy at 10 yr of follow-up.

**Endovascular Treatment vs. Medical Care Alone for Ischaemic Stroke: Systematic Review and Meta-Analysis**
BMJ 2016;353:i1754
**Purpose**: To evaluate the evidence for endovascular intervention in the treatment of ischemic stroke.
**Study**: Systematic review and meta-analysis of 10 RCTs of 2925 patients testing the efficacy and safety of adjunctive endovascular intervention vs. medical therapy, including thrombolysis, alone in patients suffering acute ischemic stroke in the anterior circulation.
**Results**: The 7 RCTs published or presented in 2015 were without significant heterogeneity and formed the basis for the analysis. The majority of patients (86%) received stent retrievers and experienced higher than expected rates of recanalization (>58%). Risk ratios for good functional outcomes were 1.56 (95%CI 1.38-1.75) and 0.86 for mortality (95% CI 0.69-1.06). There was no difference in symptomatic intracranial hemorrhage following therapy.
**Conclusions**: Endovascular therapy is safe and improves functional outcomes if added to medical care with thrombolysis and administered within 6-8 h of a large-vessel anterior circulation ischemic stroke. A trend towards improved mortality exists with complete follow-up results of several key trials pending.

# Cerebral Hemorrhage

- **definition**: intracranial bleeding into brain tissue
- **etiology**: head trauma, hemorrhagic stroke

### Investigations
- general investigations: see *Assessment and Treatment of Ischemic Stroke*, N50
- further investigations
  - LP (if suspect SAH despite negative CT)
  - may require cerebral angiogram if suspecting aneurysm or AVM
  - if typical location for hypertensive hemorrhage, repeat CT head in 4-6 wk after hemorrhage has resolved to rule out an underlying lesion

### Treatment
- medical
  - anti-hypertensives: no conclusive BP target ranges for managing ICH exist; 2010 AHA/ASA guidelines suggest that reducing sBP to as low as 140 mmHg with IV anti-hypertensives is safe and appropriate management (target sBP 140-160)
  - ICP lowering medical management (if necessary): see Neurosurgery, NS8
- surgical: see Neurosurgery, NS22

**ACE Inhibitor in Stroke Prevention – HOPE Trial**
NEJM 2000;342:145-53
**Study**: Randomized, blinded, placebo-controlled trial. Mean follow-up 5 yr.
**Patients**: 9297 patients ≥55 yr (mean age 66 yr, 73% men) who had evidence of vascular disease or DM plus one other cardiovascular risk factor and who were not known to have a low ejection fraction or heart failure.
**Intervention**: Ramipril 10 mg daily PO versus matching placebo.
**Main Outcomes**: Stroke, MI, or death from cardiovascular causes.
**Results:**

| Outcome | RRR (95%CI) | NNT (CI) |
|---|---|---|
| Stroke | 32% (16-44) | 67 (43-145) |
| MI, stroke, or CV mortality | 22% (14-30) | 26 (19-43) |
| All-cause mortality | 16% (5-25) | 56 (32-195) |

Treatment with ramipril reduced the risk of stroke (3.4% vs. 4.9%; RR 0.68; p<0.001).
**Conclusions**: In adults at high risk for cardiovascular events, ramipril reduced the risk of stroke, as well as other vascular events and overall mortality. In addition, ACEI reduce risk of stroke beyond their hypertensive effect.

# Neurocutaneous Syndromes

- see Pediatrics, P79

# Multiple Sclerosis

### Definition
- a chronic inflammatory disease of the CNS characterized by relapsing-remitting or progressive neurologic symptoms due to inflammation, demyelination, and axonal degeneration

### Clinical Patterns of MS
- relapsing-remitting (RRMS) 85%, primary progressive (PPMS) 10%, progressive relapsing (PRMS) 5%, secondary progressive (SPMS)
- benign MS (BMS): retrospective diagnosis made after 15 yr of mild disease, with no evidence of worsening (in functional ability and MRI)
- most RRMS goes on to become SPMS

### MS Variants
- **Devic's = neuromyelitis optica (NMO)**: severe optic neuritis and extensive transverse myelitis extending >3 vertebral segments (antibody positive)
- **clinically isolated syndrome (CIS)**: single MS-like episode, which may progress to MS
- **tumefactive MS**: solitary lesion >2 cm mimicking neoplasms on MRI
- **fulminant MS (Marburg)**: rapidly progressive and fatal MS associated with severe axonal damage, inflammation, and necrosis
- **pediatric MS**: onset of MS before the age of 18
  - epidemiology: rare (1.35-2.5 per 100,000 children)
  - presentation: more likely to present with isolated optic neuritis, isolated brainstem syndrome, or symptoms of encephalopathy compared to adults
  - course: 98% have RRMS
  - diagnosis and treatment similar to adult MS
  - differential diagnosis: in the setting of nonspecific CSF abnormalities and MRI evidence of white matter lesion, rule out ADEM, optic neuritis, transverse myelitis, neuromyelitis optica, CNS malignancies, leukodystrophies, and mitochondrial disease
- **acute disseminated encephalomyelitis (ADEM)**: monophasic demyelinating disorder with multifocal neurologic symptoms seen mainly in children, often following infection or vaccination

### Etiology
- **genetic**
  - polygenetic: the HLA-DRB1 gene has been demonstrated to be a genetically susceptible area
  - 30% concordance for monozygotic twins, 2-4% risk in offspring of affected mother or father
- **environmental**
  - MS is more common in regions with less sun exposure and lower stores of vitamin D (Europe, Canada, US, New Zealand, SE Australia)
  - MS has also been linked to certain viruses (e.g. EBV)

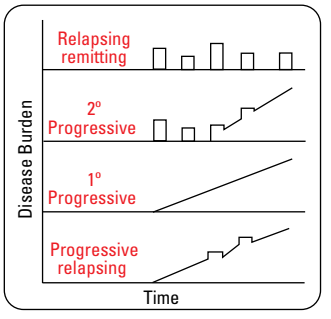


**Figure 27. Clinical patterns of MS**

Most symptoms in MS are due to cord, brainstem, and optic nerve lesions

**Chronic Cerebrospinal Venous Insufficiency (CCSVI)**
A theory proposed in 2008 described abnormal venous blood flow in patients with MS; while some RCTs are still underway, recent studies have largely discredited this highly controversial theory. That is, studies indicate no connection between CCSVI and MS

**The Expanded Disability Status Scale (EDSS)** is used as a measure of disability progression and is scored from 0 to 10 based on the neurologic exam and ambulation

## Epidemiology
- onset 17-35 yr; F:M = 3:1
- PPMS occurs in an older population with F=M

## Diagnosis for MS
- demonstration of both dissemination in time and space based on the revised McDonald criteria (2017)
  - dissemination in time: ≥2 attacks, simultaneous presence of gadolinium enhancing and non-enhancing MRI lesions at any time, or a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, presence of CSF oligoclonal bands
  - dissemination in space: ≥1 T2 lesions on MRI in at least 2 of the 4 CNS regions (periventricular, juxtacortical, infratentorial, or spinal cord) or developing a second attack that implicates a different CNS region

## Clinical Features
- symptoms include numbness, visual disturbance (optic neuritis), weakness, spasticity, diplopia (e.g. INO), impaired gait, vertigo, bladder dysfunction
- **Lhermitte's sign:** flexion of neck causes electric shock sensation down back into limbs indicating cervical cord lesion
- **Uhthoff's phenomenon**: worsening of symptoms (classically optic neuritis) in heat
- SPMS: classically presents as weakness of legs in pyramidal distribution paired with cerebellar findings of arms (i.e. intention tremor)
- symptoms not commonly found in MS: visual field defects, aphasia, apraxia, progressive hemiparesis
- relapse: acute/subacute onset of clinical dysfunction that peaks from days to weeks, followed by remission with variable symptom resolution (symptoms must last at least 24 h)
- in RRMS, average 0.4-0.6 relapses per yr, but higher disease activity in first yr of disease

## Investigations
- **MRI**: demyelinating plaques appear as hyperintense lesions on T2 weighted MRI, with active lesions showing enhancement with gadolinium
  - typical locations: periventricular, corpus callosum, cerebellar peduncles, brainstem, juxtacortical region, and dorsolateral spinal cord
  - Dawson's fingers: periventricular lesions extending into corpus callosum
  - cranial MRI is more sensitive than spinal MRI
- **CSF**: oligoclonal bands in 90%, increased IgG concentration
- **evoked potentials** (visual/auditory/somatosensory): delayed but well-preserved wave forms

## Treatment
- **acute treatment**: methylprednisolone 1000 mg IV daily x 3-7 d (no taper required); if poor response to corticosteroids, may consider plasma exchange
- **long-term treatment**: vitamin D 4000 units/d
- **disease modifying therapy (DMT)**
  - goals: decrease relapse rate, decrease progression of disability, slow accumulation of MRI lesions
  - first line: teriflunomide, interferon-β (injection: Betaseron®, Avonex®, Rebif®), glatiramer acetate (injection: Copaxone®), BG-12 (Tecfidera®)
  - second line: natalizumab (Tysabri®) (monthly IV infusion), fingolimod (Gilenya®)
  - increased risk of progressive multifocal leukoencephalopathy (PML) associated with natalizumab
  - CIS: early treatment with interferons may delay potential second attack
  - RRMS: DMT reduces rate of relapse by about 30%
  - PPMS: ocrelizumab infusion (ORATORIO trial 2017)
  - SPMS: no proven efficacy of DMTs, some evidence for interferon-β
- **symptomatic treatment**
  - spasticity: baclofen, tizanidine, dantrolene, benzodiazepine, botulinum toxin
  - bladder dysfunction: oxybutynin
  - pain: TCA, carbamazepine, gabapentin
  - fatigue: amantadine, modafinil, methylphenidate
  - depression: antidepressant, lithium
  - constipation: high fibre intake, stool softener, laxatives
  - sexual dysfunction: sildenafil (Viagra®), tadalafil (Cialis®), vardenafil (Levitra®, Staxyn®)
- **education and counselling**: MS Society, support groups, psychosocial issues

## Prognosis
- good prognostic indicators: female, young, RRMS, presenting with optic neuritis, low burden of disease on initial MRI, low rate of relapse early in disease
- PPMS: poor prognosis, higher rates of disability, poor response to therapy



**Fingolimod for Relapsing-Remitting Multiple Sclerosis**
Cochrane DB Syst Rev 2016;4:CD009371
**Purpose**: Systematic literature review of the evidence for fingolimod in treatment of relapsing-remitting MS.
**Study**: Meta-analysis of six RCTs (N=55,152 patients) investigating the benefits and harms of fingolimod and other disease modifying drugs in the treatment of relapsing-remitting MS.
**Results**: Compared to placebo and interferon beta-1a, fingolimod increases the probability of being relapse free at 24 mo (RR 1.44 vs. placebo, RR 1.18 vs. interferon β-1a) but has little to no effect on disability progression (RR 1.07 vs. placebo, RR 1.02 vs. interferon β-1a). Fingolimod use was associated with a higher incidence of adverse events and discontinuation within 6 mo.
**Conclusions**: Fingolimod significantly reduces disease activity in relapse-remitting MS compared to placebo but does not prevent disability. Its use is associated with adverse events and requires close patient monitoring, particularly within the first 6 mo. Further study is needed to assess the benefits of fingolimod versus other disease modifying drugs.



**Recombinant Interferon β or Glatiramer Acetate for Delaying Conversion of the First Demyelinating Event to Multiple Sclerosis**
Cochrane DB Syst Rev 2008;2:CD005278
**Study**: Meta-analysis of RCTs investigating clinically isolated syndrome (CIS) pateints treated with immunomodulatory drugs.
**Primary Outcomes**: Proportion of patients converting to clinically definite MS and adverse effects.
**Results**: Three trials (n=1160) tested the efficacy of interferon (IFN-α) and no trial tested glatiramer acetate (GA). The pooled odds ratio (OR) for patients on IFN versus placebo at 1 yr was 0.53 (95% CI 0.40-0.71, p<0.0001). The 2 yr follow-up OR was 0.52 (95% CI 0.38-0.70, p<0.0001). There was no significant increase in adverse events for those on IFN-α.
**Conclusions**: IFN-α treatment can delay progression to clinically definite MS in patients with CIS over 2 yr.

# Common Medications

## Table 25. Common Medications – Major Issues

| Indications | Mechanism of Action/Class | Generic Name | Trade Name | Dosing | Contraindications | Side Effects |
|---|---|---|---|---|---|---|
| **Parkinson's Disease** | Dopamine precursor | levodopa + carbidopa | Sinemet® | Carbidopa 25 mg/levodopa 100 mg PO tid<br>Maximum 200 mg carbidopa and 2000 mg levodopa/d | Narrow-angle glaucoma, use of MAO inhibitor in last 14 d, history of melanoma or undiagnosed skin lesions | Nausea, hypotension, hallucinations, dyskinesias |
| | Dopamine agonist | bromocriptine | Parlodel® | 1.25 mg PO bid, increase by 2.5 mg/d q2-4wk, up to 10-30 mg PO tid | Concomitant use of potent inhibitors of CYP3A4, uncontrolled HTN, ischemic heart disease, peripheral vascular disease; caution with renal or hepatic disease | Hypotension, N/V, dizziness, constipation, diarrhea, abdominal cramps, H/A, nasal congestion, drowsiness, hallucinations |
| | MAOB inhibitor | selegiline | Eldepryl® | 5 mg PO bid | Concomitant use of meperidine or tricyclic antidepressants | H/A, insomnia, dizziness, nausea, dry mouth, hallucinations, confusion, orthostatic hypotension, increased akinesia, risk of hypertensive crisis with tyramine-containing foods |
| **Myasthenia Gravis** | Acetylcholinesterase inhibitor | pyridostigmine | Mestinon® | 600 mg/d PO divided in 5-6 doses<br>Range 60-1500 mg/d | GI or GU obstruction | N/V, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis, diaphoresis, muscle cramps, fasciculations, muscle weakness |
| **Acute Migraine** | Triptan (selective 5-hydroxytryptamine receptor agonist) | sumatriptan | Imitrex® | 25-100 mg PO prn, maximum 200 mg/d | Hemiplegic/basilar migraine, ischemic heart disease, CVD, uncontrolled HTN, use of ergotamine/5-HT1 agonist in past 24 h, use of MAO inhibitor in last 14 d, severe hepatic disease | Vertigo, chest pain, flushing, sensation of heat, hypertensive crisis, peripheral vascular disease, coronary artery vasospasm, cardiac arrest, nausea, vomiting, H/A, hyposalivation, fatigue |
| | Ergot (5-HT1D receptor agonist) | dihydroergotamine | Migranal® | Nasal spray 0.5 mg/spray, maximum 4 sprays/d | Hemiplegic/basilar migraine, high-dose ASA therapy, uncontrolled HTN, ischemic heart disease, peripheral vascular disease, severe hepatic or renal dysfunction, use of triptans in last 24 h, use of MAO inhibitors in last 14 d | Coronary artery vasospasm, transient myocardial ischemia, MI, ventricular tachycardia, ventricular fibrillation; may cause significant rebound H/A |
| **Migraine Prophylaxis** | Anticonvulsant | topiramate | Topamax® | 25 mg PO OD (in evening); may increase weekly by 25 mg/d to a max 50 mg bid | | Sedation, mood disturbance, cognitive dysfunction, anorexia, nausea, diarrhea, paresthesias, metabolic acidosis, glaucoma, SJS/TEN |
| | β-blocker | propranolol | Inderal® | 80 mg/d divided every 6-8 h; increase by 20-40 mg/dose every 3-4 wk to max 160-240 mg/d in divided doses q6-8h | Uncompensated CHF, severe bradycardia or heart block, severe COPD or asthma | Fatigue, cognitive dysfunction, disturbed sleep, rashes, dyspepsia, dry eyes, heart failure, bronchospasm, risk of acute tachycardia and HTN if withdrawal |
| **Epilepsy** | Anticonvulsant for partial ± 2º generalization, generalized tonic-clonic | carbamazepine | Tegretol® | Start at 100-200 mg PO OD-tid, increase by 200 mg/d up to 800-1200 mg/d | History of bone marrow depression, hepatic disease, hypersensitivity to the drug, use of MAO inhibitor in last 14 d | Drowsiness, H/A, unsteadiness, dizziness, N/V, skin rash, agranulocytosis/aplastic anemia (rare) |
| | Anticonvulsant for partial, tonic-clonic, status epilepticus | phenytoin | Dilantin® | 100 mg PO tid, maintenance dose up to 200 mg PO tid<br>SE: 10-15 mg/kg IV loading dose then maintenance doses of 100 mg PO or IV q6-8h | Hypersensitivity, pregnancy, breastfeeding; caution with P-450 interactions | Hypotension, SJS/TEN, SLE-type symptoms, gingival hypertrophy, peripheral neuropathy, H/A, blood dyscrasias, nystagmus, N/V, constipation, sedation, teratogenic |
| | Anticonvulsant for partial or generalized, absence seizures | valproic acid | Depakene® Apo-Valproic® | 10-15 mg/kg/d PO in divided doses, increase incrementally until therapeutic dose to max of 60 mg/kg/d | Hypersensitivity, hepatic disease, urea cycle disorders | Hepatic failure, H/A, somnolence, alopecia, N/V, diarrhea, tremor, diplopia, thrombocytopenia, hypothermia, pancreatitis, encephalopathy |
| | Anticonvulsant for absence seizures | ethosuximide | Zarontin® | 500 mg/d PO, increase by 250 mg every 4-7 d to max 1.5 g/d in divided doses | Hypersensitivity (succinimides) | CNS depression, blood dyscrasias, SLE, SJS, GI symptoms |
| **Stroke Prevention in Atrial Fibrillation** | Anticoagulant (direct thrombin inhibitor) | dabigatran | Pradaxa® | 110 mg PO bid or 150 mg PO bid | CrCl <30 mL/min, significant hemostatic impairment, or CNS lesions within 6 mo with high risk of bleeding | Dyspepsia, gastritis, bleeding |
| | Anticoagulant (Factor Xa inhibitor) | rivaroxaban | Xarelto® | 15 mg PO daily or 20 mg PO daily | Concomitant anticoagulant, hepatic disease, pregnancy, strong CYP3A4 and P-gp inhibitors e.g. itraconazole, ritonavir | Bleeding |
| | Anticoagulant (Factor Xa inhibitor) | apixaban | Eliquis® | 2.5 mg PO bid or 5 mg PO bid | Active bleeding, gastrointestinal bleeding, recent cerebral infarction, active peptic ulcer disease with recent bleeding, hepatic disease with coagulopathy | Bleeding (conjunctival, gastrointestinal, gingival, contusion, hematoma, epistaxis, hematuria) |

**Table 25. Common Medications – Major Issues** (continued)

| Indications | Mechanism of Action/Class | Generic Name | Trade Name | Dosing | Contraindications | Side Effects |
|---|---|---|---|---|---|---|
| **Mild to Moderate Alzheimer's Disease or Dementia with Lewy Bodies** | Cholinesterase Inhibitor | donepezil | Aricept® | 5 mg PO OD, may increase to 10 mg PO OD after 4-6 wk | Hypersensitivity to donepezil or to piperidine derivatives | Diarrhea, N/V, insomnia, muscle cramps, fatigue, anorexia, HTN, syncope, AV block |
| **Multiple Sclerosis** | MS Disease Modifying Therapy | interferon-β-1b<br>interferon-β-1a SC<br>interferon-β-1a IM | Betaseron®<br>Rebif®<br>Avonex® | 0.25 mg (8 MU) SC every other day<br>44 µg SC 3 times/wk<br>30 µg IM once weekly | Pregnancy, hypersensitivity to natural or recombinant interferon-β | Injection site reactions, injection site necrosis, flu-like symptoms (fever, chills, myalgia; tend to decrease over time) |
| | MS Disease Modifying Therapy | glatiramer acetate | Copaxone® | 20 mg SC OD | Hypersensitivity to glatiramer or mannitol | Injection site reactions, nausea, transient chest pain, vasodilation |
| | MS Disease Modifying Therapy | natalizumab | Tysabri® | 300 mg IV given over 1 h, every 4 wk | Hypersensitivity to natalizumab, progressive multifocal leukoencephalopathy (PML) | Rash, nausea, arthralgia, H/A, infections, rare risk of PML and melanoma |
| | MS Disease Modifying Therapy | fingolimod | Gilenya® | 0.5 mg PO OD | Not available | Diarrhea, transaminitis, H/A, bradyarrhythmia, lymphopenia |
| **Spasticity (i.e. MS)** | Muscle Relaxant – Antispastic | baclofen | Lioresal® | 5 mg PO tid, increase by 15 mg/d q3d<br>to max dose 80 mg/d in three divided doses | Hypersensitivity to baclofen | Transient drowsiness, daytime sedation, dizziness, weakness, fatigue, convulsions, constipation, nausea |

# Landmark Neurology Trials

| Trial | Reference | Results |
|---|---|---|
| NASCET | *NEJM* 1991;7:445-53 | Patients with symptomatic carotid stenosis of 70-99% benefited more from carotid endarterectomy than best medical therapy |
| Interferon-β Multiple Sclerosis Study Group Trial | *Neurology* 1993;43:655-61 | Interferon-β-1b reduces relapse rate and severity of relapses in RRMS |
| NINDS rtPA | *NEJM* 1995;333:1581-7 | rtPA reduces mortality and long-term disability when administered within 3 h of acute stroke |
| SPARCL | *NEJM* 2006;355:549-59 | The observed benefit of statins in cardiovascular disease is also extended to patients with a recent stroke or TIA |
| ECASS 3 | *NEJM* 2008;359:1317-29 | rtPA improved clinical outcomes when administered within 3 to 4.5 h of acute ischemic stroke |
| PROFESS | *NEJM* 2008;359:1238-51 | ASA + dipyridamole and clopidogrel showed similar benefits in secondary stroke prevention |
| RELY | *NEJM* 2009;361:1139 | Dabigatran superior to warfarin for stroke prevention in patients with AF |
| ROCKET-AF | *NEJM* 2011;365:883-91 | Rivaroxaban noninferior to warfarin for stroke prevention in patients with AF |
| ERS | *NEJM* 2011;365:981-92 | Apixaban superior to warfarin for stroke prevention in patients with AFT |
| CREST | *NEJM* 2010;363:11-23 | Carotid stenting and endarterectomy had similar benefits in reduction of stroke, MI, and death in carotid stenosis, but in the periprocedural period, stenting had a higher rate of stroke, while endarterectomy had a higher rate of MI |
| INTERACT2 | *NEJM* 2013;368:2355-65 | Intensive lowering of blood pressure (sBP<140) in spontaneous intracerebral hemorrhage did not improve mortality or severe disability but improved functional outcomes (odds ratio for greater disability 0.87, 95% CI 0.77-1.00, p=0.04) |
| MR CLEAN | *NEJM* 2015;372:11-20 | Intra-arterial treatment (intra-arterial thrombolysis, mechanical treatment, or both) for emergency revascularization administered within 6 h after stroke onset was effective and safe for acute ischemic stroke caused by proximal intracranial occlusion of the anterior circulation |

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# NS Neurosurgery

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# Acronyms

| | |
|---|---|
| AIDS | acquired immunodeficiency syndrome |
| AVF | arteriovenous fistula |
| AVM | arteriovenous malformation |
| BBB | blood brain barrier |
| BUN | blood urea nitrogen |
| C&S | culture and sensitivity |
| CBF | cerebral blood flow |
| CNS | central nervous system |
| CPA | cerebellar pontine angle |
| CPP | cerebral perfusion pressure |
| CSF | cerebral spinal fluid |
| CVR | cerebral vascular resistance |
| DBS | deep brain stimulation |
| DI | diabetes insipidus |
| ECF | extracellular fluid |
| ECT | electroconvulsive therapy |
| EEG | electroencephalography |
| EMG | electromyography |
| EVD | external ventricular drain |
| GCS | Glasgow coma scale |
| GPi | globus pallidus pars interna |
| HTN | hypertension |
| H/A | headache |
| IC | internal capsule |
| ICF | intracellular fluid |
| ICH | intracerebral hemorrhage |
| ICP | intracranial pressure |
| ICU | intensive care unit |
| IVH | intraventricular hemorrhage |
| LMN | lower motor neuron |
| LOC | loss of consciousness |
| LP | lumbar puncture |
| MAP | mean arterial pressure |
| MLS | midline shift |
| MRA | magnetic resonance angiography |
| N/V | nausea/vomiting |
| NC | neurogenic claudication |
| NICU | neonatal intensive care unit |
| NPH | normal pressure hydrocephalus |
| OPLL | ossification of posterior longitudinal ligament |
| PAG | periaqueductal grey matter |
| PET | positron emission tomography |
| PLL | posterior longitudinal ligament |
| PNET | primitive neuroectodermal tumour |
| PVG | periventricular grey matter |
| SAH | subarachnoid hemorrhage |
| SCI | spinal cord injury |
| SDH | subdural hemorrhage |
| SIADH | syndrome of inappropriate antidiuretic hormone |
| SPECT | single photon emission computed tomography |
| SRS | stereotactic radiosurgery |
| STN | subthalamic nucleus |
| UMN | upper motor neuron |
| VPL | ventral posterolateral |
| VPM | ventral posteromedial |
| WBRT | whole brain radiation therapy |

See Functional Neuroanatomy Software

# Basic Anatomy Review

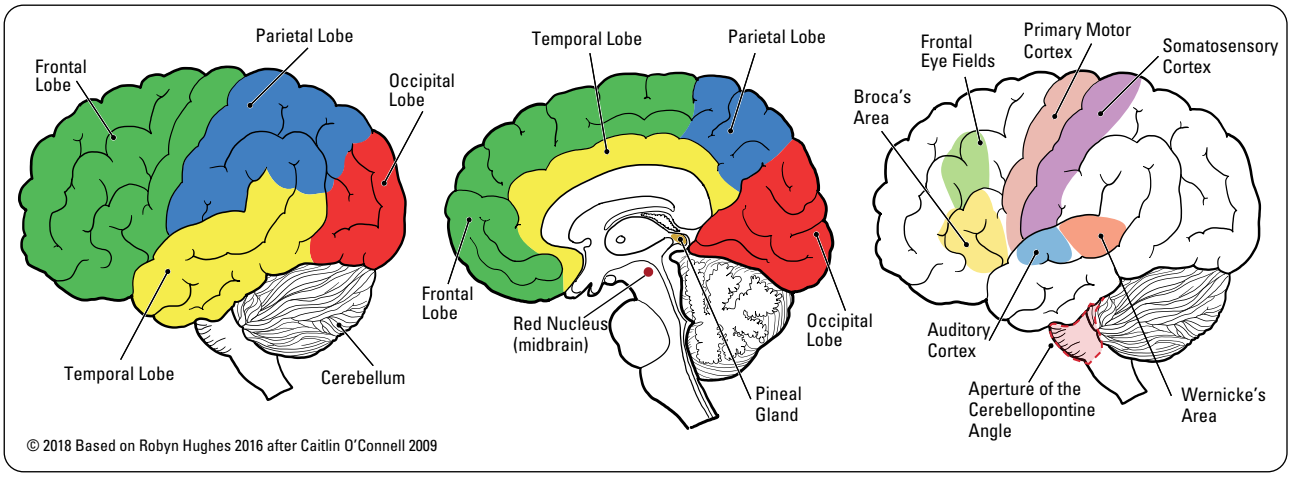



**Figure1. Basic surface anatomy**

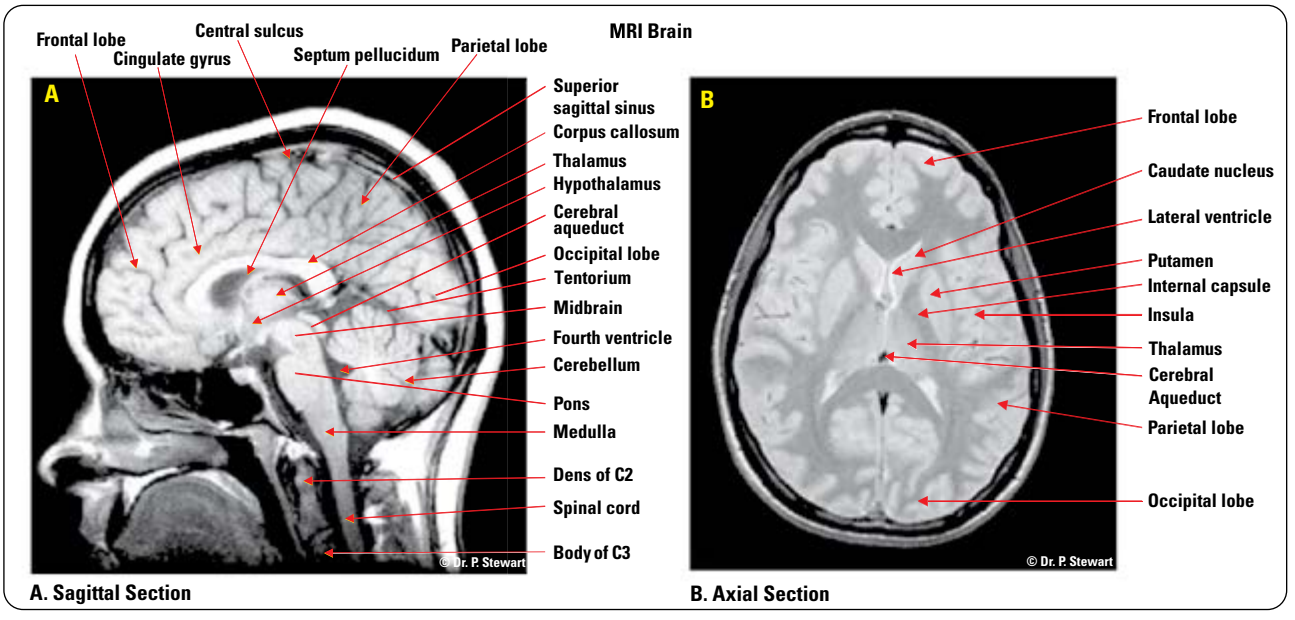



**Figure 2. Magnetic resonance imaging (MRI) neuroanatomy. The left panel is a T1-weighted image; the right panel is T2-weighted**
Stewart P, et al. Functional Neuroanatomy (Version 2.1). Health Education Assets Library 2005

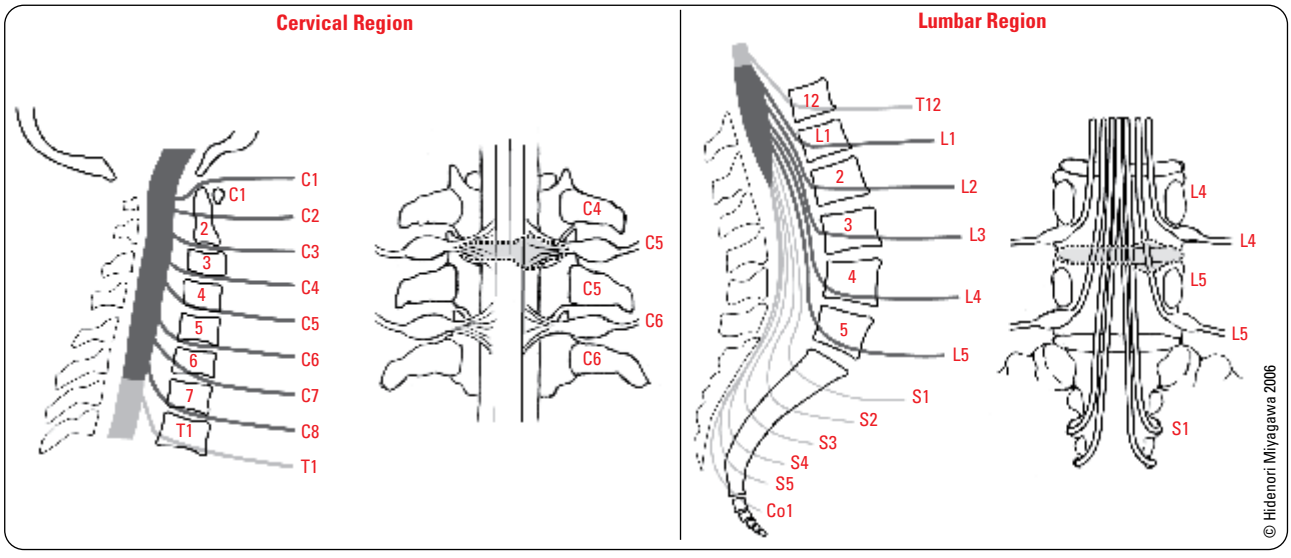



**Figure 3. Relationship of nerve roots to vertebral level in the cervical and lumbar spine**
Note: AP views depict left-sided C4-5 and L4-5 disc herniation, and correlating nerve root impingement

**Artery legend:**
1. Anterior cerebral
2. Anterior communicating
3. Internal carotid
4. Middle cerebral
5. Posterior communicating
6. Posterior cerebral
7. Superior cerebellar
8. Basilar
9. Pontine
10. Anterior inferior cerebellar
11. Vertebral
12. Posterior inferior cerebellar
13. Anterior spinal
14. Posterior spinal
15. Anterior choroidal
16. Medial lenticulostriate
17. Lateral lenticulostriate
18. Penetrating branches of posterior spinal artery (P1 segment)

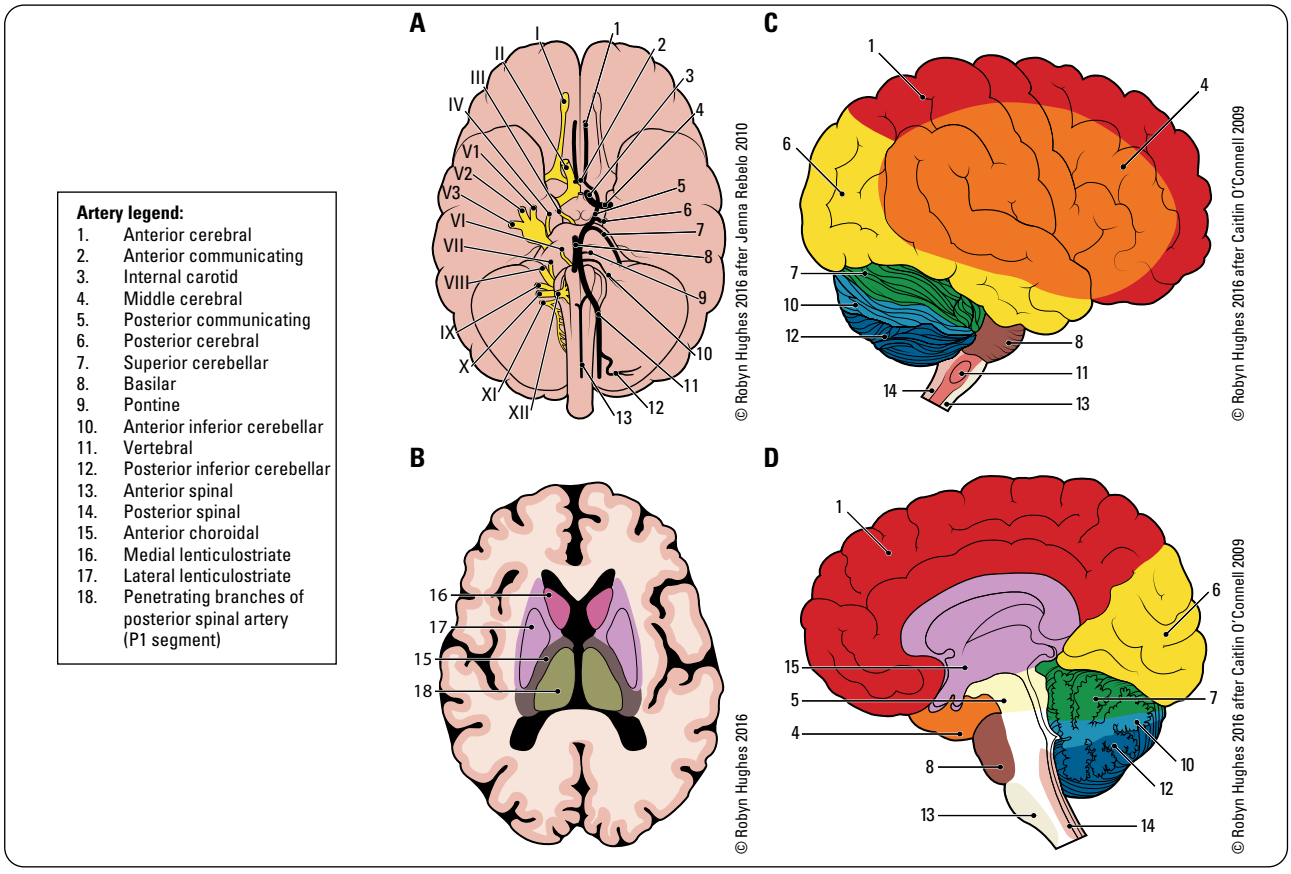



**Figure 4. Vascular supply of the brain**
Please see legend for artery names. 4A. Circle of Willis, most common variant. 4B. Vascular territories of the brain and brainstem, sagittal view, seen laterally. 4C. Vascular territories of the brain and brainstem, sagittal view, seen medially

# Differential Diagnoses of Common Presentations

| Intracranial Mass Lesions | Disorders of the Spine | Peripheral Nerve Lesions |
|---|---|---|
| **Tumour**<br>Metastasis<br>Astrocytoma<br>Meningioma<br>Vestibular schwannoma (acoustic neuroma)<br>Pituitary adenoma<br>Primary CNS lymphoma<br><br>**Pus/Inflammation**<br>Cerebral abscess, extradural abscess, subdural empyema<br>Encephalitis (see Infectious Diseases, ID16)<br>Tumefactive MS<br><br>**Blood**<br>Extradural (epidural) hematoma<br>Subdural hematoma<br>Ischemic stroke<br>Hemorrhage: SAH, ICH, IVH<br><br>**Cyst**<br>Arachnoid cyst<br>Dermoid cyst<br>Epidermoid cyst<br>Colloid cyst (3rd ventricle) | **Extradural**<br>Degenerative: disc herniation, canal stenosis, spondylolisthesis/spondylolysis<br>Infection/inflammation: osteomyelitis, discitis<br>Ligamentous: OPLL<br>Trauma: mechanical compression/instability, hematoma<br>Tumours (55% of all spinal tumours): lymphoma, metastases (lymphoma, lung, breast, prostate), neurofibroma<br><br>**Intradural Extramedullary**<br>Vascular: dural AVF, subdural hematoma (especially if on anticoagulants)<br>Tumours (40% of all spinal tumours): meningioma, schwannoma, neurofibroma<br><br>**Intradural Intramedullary**<br>Tumours (5% of all spinal tumours): astrocytomas, ependymomas, hemangioblastomas, and dermoids<br>Syringomyelia: trauma, congenital, idiopathic<br>Infectious/inflammatory: TB, sarcoid, transverse myelitis<br>Vascular: AVM, ischemia | **Neuropathies**<br>Traumatic<br>Entrapments<br>Iatrogenic<br>Inflammatory<br>Tumours |

# INTRACRANIAL PATHOLOGY

## Intracranial Pressure Dynamics

**Table 1. Approach to Intracranial Pathology**

| Issue | Time Frame | Features |
|---|---|---|
| **Vascular** | Sudden | No H/A = occlusive<br>H/A = hemorrhagic |
| **Metabolic** | Hours to days | Affects entire CNS |
| **Infectious** | Days to weeks | Often a source of infection or immunodeficiency on history |
| **Tumour** | Months | Increased ICP:<br>Initially → H/A<br>Constant<br>Progressive<br>Severe<br>Worse in morning and/or wakes from sleep<br>As ICP increases:<br>Blurry vision<br>Projectile vomiting (may initially present without nausea)<br>Severely raised ICP:<br>Cushing's reflex<br>1. Bradycardia<br>2. HTN<br>3. Respiratory irregularity |

**Table 2. Consequences of Common Brain Lesions**

| Location of Lesion | Consequence |
|---|---|
| **Frontal Lobe**<br>Usually large lesions produce symptoms | Abulia, disinhibition, apathy, executive dysfunction, deficits in orientation and judgment, ± primitive reflex re-emergence, ± contralateral UMN signs (upgoing Babinski reflex and pronator drift) |
| **Frontal Eye Fields** | Gaze deviation toward side of a destructive lesion<br>Gaze deviation away from irritative lesion (i.e. seizure) |
| **Broca's Area**<br>Posterior inferior frontal gyrus of dominant hemisphere | Non-fluent, dysarthric, aphasia<br>Repetition impaired<br>Comprehension spared |
| **Occipital Lobe** | Contralateral homonymous hemianopsia |
| **Parietal Lobe**<br>Either side<br>Dominant side (Left)<br>Non-dominant side (Right) | Dressing apraxia, cortical sensory loss, lower homonymous quadrantanopia<br>Inattention or extinction of non-dominant side<br>Aphasias, Gerstmann's syndrome<br>Hemispatial neglect, apraxias, agnosias (if temporal involvement) |
| **Temporal Lobe** | Hippocampus: anterograde amnesia<br>Upper homonymous hemianopia<br>Wernicke's aphasia (if left/dominant side) |
| **Wernicke's Area**<br>Posterior superior temporal gyrus of dominant hemisphere | Fluent aphasia<br>Repetition impaired<br>Comprehension impaired |
| **Basal Ganglia** | Resting tremor<br>Chorea<br>Athetosis<br>Hemiplegia if internal capsule involved |
| **Subthalamic Nucleus** | Contralateral hemiballismus |
| **Brainstem** | Absent brainstem reflexes: oculocephalic, oculovestibular, corneal, gag, and cough<br>Dorsal midbrain/pineal gland: Parinaud's syndrome (supranuclear upward gaze palsy)<br>Pons: locked-in syndrome<br>Below red nucleus: decerebrate posture<br>Above red nucleus: decorticate posture<br>Reticular activating system (midbrain): reduced level of arousal<br>Cerebellar pontine angle: disequilibrium, ataxia, and other CN V,VII,VIII deficits |
| **Cerebellar Hemisphere** | Intention tremor<br>Ipsilateral limb ataxia<br>Fall towards side of lesion |
| **Cerebellar Vermis** | Truncal ataxia<br>Dysarthria |

# ICP/Volume Relationship

- Monro-Kellie Doctrine: the brain is encased in a rigid skull with constant intracranial volume consisting of CSF, blood, and brain
- the increase in one constituent will: 1) necessitate the redistribution of CSF, blood, and/or brain and 2) increase ICP
- compensatory mechanisms initially maintain a normal ICP
- compensatory reserve (spatial compensation): 60-80 mL in young people, 100-140 mL in elderly (largely due to cerebral atrophy)
  - **immediate**: egression of CSF through foramen magnum to spinal canal, displacement of venous blood from sinuses into jugular veins
- once compensation is exhausted, ICP rises exponentially:
  - **late**: displacement of arterial blood (decreased CPP) eventually leading to ischemia, increasing brain edema, or expanding mass displaces parenchyma into compartments under less pressure (Table 3)
  - **end**: cessation of cerebral perfusion when ICP>MAP, cerebral herniation down into foramen magnum

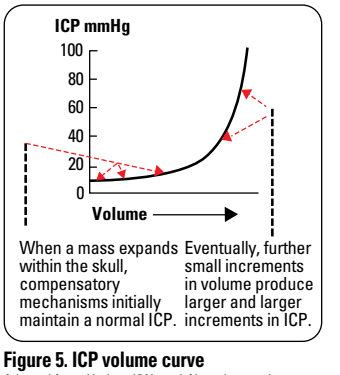



**Figure 5. ICP volume curve**
Adapted from: Lindsay KW, et al. Neurology and neurosurgery illustrated. © 2004. With permission from Elsevier

# Cerebral Blood Flow

- brain receives about 15% of cardiac output (~750 mL/min)
- CBF is the vital parameter for brain function, it depends on CPP and CVR
- CPP is the difference between MAP and ICP (normal CPP >50 mmHg)
- cerebral autoregulation: mechanism that maintains constant CBF despite changes in CPP, unless:
  - high ICP such that CPP <40 mmHg
  - MAP >150 mmHg or MAP <50 mmHg (these setpoints can be higher in hypertensives, thus important to avoid hypotension)
  - increased $CO_2$ = increased CBF via vasodilation
  - $O_2$ <50 mmHg = increased CBF via vasodilation
  - brain injury: e.g. SAH, severe trauma

CBF = CPP / CVR
CPP = MAP – ICP

**MAP Targets in Trauma**
Traumatic brain injury (TBI): MAP >80 mmHg
Spinal cord injury (SCI): MAP between 85-90 mmHg in first 7 d post injury

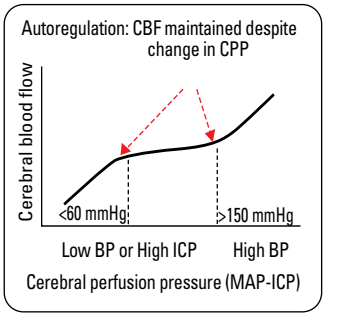



**Figure 6. Cerebral autoregulation curve**
Adapted from: Lindsay KW, et al. Neurology and neurosurgery illustrated. © 2004. With permission from Elsevier

# ICP Measurement

- normal ICP 10-15 mmHg for adult, 3-7 mmHg for child, 1.5-6 mmHg for infant; varies with patient position
- moderate elevation >20 mmHg
- severe elevation >40 mmHg

### Acute Monitoring
- indications include: severe TBI (GCS <8T) + abnormal CT; normal CT if two or more of age >40, blood pressure <90 mmHg, or abnormal motor posturing
- methods: intraventricular catheter (external ventricular drain) is the "gold standard"; most accurate method and allows therapeutic drainage of CSF. Non-invasive methods (including transcranial Doppler, CT/MRI, fundoscopy etc) fail to measure ICP accurately enough to be used as routine measurement techniques

### Chronic Monitoring
- fibre-optic monitor (intraventricular, intraparenchymal, subdural), subarachnoid bolt (Richmond screw), and epidural monitor

# Elevated ICP

### Etiology
- pathologic structure
  - intracranial mass (tumour, cyst)
  - cerebral edema
    - vasogenic: BBB compromised (meningitis, hypertensive encephalopathy, tumour, late ischemia)
    - cytotoxic: BBB intact (cell death in: early ischemia, brain injury, encephalitis, status epilepticus)
    - interstitial: transudation of CSF into peri-ventricular white matter in hydrocephalus
    - osmotic: osmotic gradient increases intracellular free $H_2O$ (acute hyponatremia, hepatic encephalopathy)
  - other space occupying lesions: depressed skull fracture, foreign body, pus/empyema
- increased intracranial blood volume
  - space occupying blood: epidural and subdural hematomas, intraparenchymal and SAHs
  - venous obstruction (venous sinus thrombosis, superior vena cava syndrome, cor pulmonale, venous sinus compression)
  - impaired autoregulation (hypotension, HTN, brain injury, status epilepticus)
  - vasodilatation (increased $pCO_2$/decreased $pO_2$/decreased extracellular pH)
- **increased intracranial CSF volume** (see *Hydrocephalus*, Table 6, NS9)
  - non-obstructive: increased production (rare, choroid plexus papilloma), decreased absorption
  - obstructive: blockage in CSF pathway
- **idiopathic intracranial HTN** (pseudotumour cerebri) – see *Idiopathic Intracranial Hypertension*, NS8

Lumbar puncture can be used for ICP monitoring, though it is not the most accurate. LP can precipitate tonsillar and uncal herniation with elevated ICP and is absolutely contraindicated with known/suspected intracranial mass

**Consider Monitoring ICP in the following Situations**
- Patients with an abnormal head CT (SAH, hematoma, contusion, basal cistern compression, swelling, and herniation), and GCS score ≤8 after CPR

Or
- Patients with a normal head CT and GCS score of ≤8 AND the presence of two or more of the following:
  - >40 yr
  - Unilateral or bilateral motor posturing
  - sBP <90 mmHg
  - Post-operative monitoring
  - Investigation of NPH

**Cautioned Medication Use in Elevated ICP**
- Nitroprusside – can raise ICP in patients with intracranial mass lesions due to direct vasodilation (arterial>venous)
- Nitroglycerine – can raise ICP via vasodilation but less so than nitroprusside because venous>arterial
- Succinylcholine – induced fasciculations may increase ICP

## Clinical Features

### Table 3. Clinical Features of Elevated ICP

| Clinical Features | Acutely Elevated ICP | Chronic Progressive ICP Elevation |
|---|---|---|
| **Headache** | Both aggravated by stooping, coughing, and straining<br>Morning H/A: vasodilatation due to increased $CO_2$ with recumbency | |
| **Nausea and Vomiting** | Present in both, though greater predilection in acutely elevated ICP | |
| **Level of Consciousness** | Lethargy if ICP = dBP or midbrain compression | Irritability, inattentiveness. Normal or modestly reduced LOC, confusion |
| **GCS** | Significant decline in GCS<br>Best index to monitor progress and predict outcome of acute intracranial process (see *Neurotrauma*, NS30) | Can be unchanged or modestly decreased |
| **Optic Disc Changes** | Subtle changes suggesting papilledema (subtle elevations in disc margin, mild disc hyperemia) ± retinal hemorrhages (may take 24-48 h to develop) | Obvious papilledema |
| **Visual Changes** | Less common. Often not affected initially, however visual obscurations, flickering, or blurring can occur | Optic atrophy/blindness due to chronic papilledema<br>Enlarged blind spot, if advanced → episodic constrictions of visual fields ("grey-outs" lasting ~20 min)<br>Differentiate from papillitis (usually unilateral with decreased visual acuity) |
| **Extra-Ocular Movements** | Less common. CN VI palsy: due to long intracranial course, more sensitive to ICP changes and thus earlier sign of acutely increased ICP<br>Often falsely localizing (causative lesion remote to nerve)<br>**Upward gaze palsy and sunset eyes** (especially in children with obstructive hydrocephalus) | Often full extraocular movement |
| **Herniation Syndromes** | Often occur | Present if acute on chronic presentation |
| **Neurologic Deficits** | Focal deficits present | Focal deficits can be present |

**Blood Brain Barrier**
Glucose and amino acids cross slowly
Non-polar/lipids cross fast

Infarction/neoplasm → destroy tight junctions → vasogenic edema

**Cushing's Triad of Acute Raised ICP**
(full triad seen in 1/3 of cases)
- Hypertension
- Bradycardia (late finding)
- Irregular respiratory pattern

**Papilledema**
- Optic disc swelling with blurred margins (most commonly bilateral)
- Larger blind spot

### Investigations
- patients with suspected elevated ICP require an urgent CT/MRI to identify etiology, assess for midline shift/herniation
- ICP monitoring where appropriate

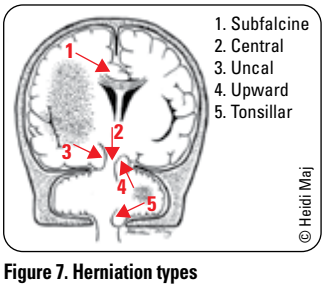



**Figure 7. Herniation types**

# Herniation Syndromes

### Table 4. Herniation Syndromes

| Herniation Syndrome | Definition | Etiology | Clinical Features |
|---|---|---|---|
| **1. Subfalcine** | Cingulate gyrus herniates under falx | Lateral supratentorial lesion | Usually asymptomatic<br>Warns of impending transtentorial herniation<br>Risk of ACA compression |
| **2. Central Tentorial (Axial)** | Displacement of diencephalon through tentorial notch | Supratentorial midline lesion<br>Diffuse cerebral swelling<br>Late uncal herniation | Small pupils, moderately dilated, fixed (rostral to caudal deterioration), sequential failure of diencephalon, medulla<br>Decreased LOC (midbrain compression), EOM/upward gaze impairment ("sunset eyes"): compression of pretectum and superior colliculi (Parinaud's syndrome)<br>Risk of PCA compression<br>Brainstem (Duret) hemorrhage: secondary to shearing of basilar artery perforating vessels<br>Diabetes insipidus (traction on pituitary stalk and hypothalamus), end-stage sign |
| **3. Lateral Tentoria (Uncal)** | Uncus of temporal lobe herniates down through tentorial notch | Lateral supratentorial lesion (often rapidly expanding traumatic hematoma) | Ipsilateral non-reactive dilated pupil (earliest, most reliable sign) + ipsilateral EOM paralysis, ptosis (CN III compression)<br>Decreased LOC (midbrain compression)<br>Risk of PCA compression<br>Contralateral hemiplegia ± extensor (upgoing) plantar response<br>± ipsilateral hemiplegia ("Kernohan's notch" – a false localizing sign resulting from pressure from the edge of the tentorium on the contralateral cerebral peduncle) |
| **4. Upward** | Cerebellar vermis herniates through tentorial incisura | Posterior fossa mass, brainstem or cerebellar infarction, exacerbated by ventriculostomy or VP shunt | Cerebellar infarct (superior cerebellar artery [SCA] compression)<br>Hydrocephalus (cerebral/sylvian aqueduct compression) |
| **5. Tonsillar** | Cerebellar tonsils herniate through foramen magnum | Infratentorial lesion<br>Following central tentorial herniation<br>Following LP in presence of intracranial mass lesion | Neck stiffness and head tilt (tonsillar impaction)<br>Decreased LOC (midbrain compression)<br>Flaccid paralysis<br>Respiratory irregularities, respiratory arrest (compression of medullary respiratory centres)<br>Blood pressure instability (compression of medullary cardiovascular centres) |

# Treatment of Elevated ICP

- treatment principle: treat primary etiology (i.e. remove mass lesions, ensure adequate ventilation for example in ARDS)
- if elevated ICP persists following treatment of primary cause, consider therapy when ICP >20 mmHg
- targets: ICP <22 mmHg, CPP 60-70 mmHg, sBP >100 (age 50-69) or >110 (age <50 or >70) mmHg (individualize targets based on patient's clinical picture and progression)

**Table 5. Management of Elevated ICP**

| Consideration | Intervention | Rationale |
|---|---|---|
| **Conservative Measures** | | |
| **Position** | Elevate head of bed at 30°<br>Maintain neck in neutral position | Increases<br>1. Jugular venous patency<br>2. intracranial venous outflow with minimal effect on MAP |
| **Fever Management** | Acetaminophen or mechanical cooling | Decrease metabolic demands to decrease CBF and minimize brain injury |
| **Prevent Hypotension** | PRN: fluid, vasopressors, dopamine, norepinephrine | Maintains CBF |
| **Normocarbia** | Ventilate to $pCO_2$ 35-40 mmHg | Prevents vasodilatation |
| **Adequate $O_2$** | Target $pO_2$ >60 mmHg | Prevents hypoxic brain injury |
| **Osmolar Diuresis** | Mannitol 20% IV solution 1-1.5 g/kg, then 0.25 g/kg q6h to serum osmolarity of 315-320<br>Acts in 15-30 min, maintain sBP >100 mmHg<br>3% hypertonic saline comparable to mannitol | Increase serum tonicity → osmotically drives fluid out of brain |
| **Corticosteroids** | Dexamethasone | Decrease vasogenic edema over subsequent days around brain tumour, abscess, blood<br>No proven value in head injury or stroke |
| **Aggressive Measures** | | |
| **Sedation** | Usually Propofol<br>Others: barbituates/codeine, or fentanyl/$MgSO_4$<br>Light = barbituates/codeine<br>Heavy = fentanyl/$MgSO_4$ | Reduces sympathetic tone<br>Reduces HTN induced by muscle contraction |
| **Paralysis** | Vecuronium | Reduces sympathetic tone<br>Reduces HTN induced by muscle contraction |
| **Barbiturate-Induced Coma (refractory ICP)** | Phentobarbital 10 mg/kg over 30 min, then 1 mg/kg q1h continuous infusion | Reduce CBF and metabolism<br>Decreases mortality, but no affect on neurologic outcome<br>No role for the use of hypothermia in head injury |
| **Hyperventilate** | Target $pCO_2$ 30-35 mmHg<br>Avoid within 24 h following trauma | Decreases CBF and thus ICP but use for brief periods only |
| **Drain CSF** | Insert EVD (if acute) or shunt<br>Drain 3-5 mL CSF | Reduces intracranial volume |
| **Decompression** | Decompressive craniectomy | Allows brain to swell while reducing risk of herniation |

**Treatment of Elevated ICP**

**ICP HEAD**
**I**ntubate
**C**alm (sedate)/**C**oma
**P**lace drain/**P**aralysis
**H**yperventilate
**E**levate head
**A**dequate BP
**D**iuretic (mannitol)

**Trial of Decompressive Craniectomy for Traumatic Intracranial Hypertension**
N Engl J Med 2016;375:1119-30
**Methods**: RCT comparing decompressive craniectomy to barbiturate coma and medical management in 400 patients with TBI and refractory intracranial hypertension. Primary outcome was Extended Glasgow Outcome Scale at 6 mo.
**Results**: Patients treated with decompressive craniectomy had lower mortality rates (26.9% vs. 48.9%) but higher rates of disability (8.5% v. 2.1% lower severe disability, 21.9% v. 14.4% upper severe disability, 15.4% v. 8.0% moderate disability).
**Conclusion**: Compared to medical care, decompressive craniectomy in patients with TBI and refractory intracranial hypertension results in lower mortality and higher rates of vegetative state and severe disability.

# Idiopathic Intracranial Hypertension (Pseudotumour Cerebri)

## Definition
- raised ICP with papilledema, but without: mass, hydrocephalus, infection, or hypertensive encephalopathy (diagnosis of exclusion)
- diagnosed by modified Dandy's criteria

## Etiology
- unknown (majority), but associated with:
  - dural sinus thrombosis
  - **habitus/diet**: obesity, hypervitaminosis A
  - **endocrine**: reproductive age, menstrual irregularities, Addison's/Cushing's disease
  - **hematologic**: iron deficiency anemia, polycythemia vera
  - **drugs**: steroid withdrawal, tetracycline, amiodarone, lithium, nalidixic acid, oral contraceptive, growth hormone, retinoids
- risk factors overlap with those of venous sinus thrombosis; similar to those for gallstones ("fat, female, fertile, forties")

## Epidemiology
- incidence: general population ~1-2/100,000/yr; obese women of childbearing age 19-21/100,000

## Clinical Features
- **symptoms**: H/A in >90%, nausea, transient visual obscurations, pulsatile tinnitus, diplopia can occur with CN VI palsy, neck/back pain
- **signs**: CN VI palsy can occur (otherwise no neurologic deficits), visual acuity and field deficits, papilledema, optic atrophy
- **morbidity**: risk of blindness and severe visual impairment are the major morbidity of IHH (6-24%

**Modified Dandy's Criteria**
1. Symptoms of raised ICP
2. No localizing signs except sixth nerve palsy
3. Patient awake and alert
4. Normal neuroimaging without evidence of thrombosis
5. LP opening pressure >25 cm $H_2O$, normal CSF
6. No better explanation for raised ICP

risk), but are not reliably correlated to duration, symptoms or clinical course
- **clinical course**: usually self-limited, recurrence in 10%, chronic in some

### Investigations
- **MRI-brain** (with and without contrast): slit like ventricles and distended perioptic subarachnoid space, but otherwise normal
  - rule out: venous sinus thrombosis, mass, infection, hydrocephalus
- **LP findings**
  - opening pressure >25 cm $H_2O$
  - normal CSF analysis
- **ophthalmologic**: fields, acuity, papilledema

### Treatment
- **lifestyle change**: encourage weight loss, fluid/salt restriction
- **pharmacotherapy**: acetazolamide (decreases CSF production), thiazide diuretic, or furosemide; discontinue offending medications
- **surgery**: if above fail, serial LPs (temporizing), shunts, optic nerve sheath fenestration (if progressive impairment of visual acuity)
- **long term**: 2 yr follow-up, repeat imaging to rule out occult tumour, ophthalmology follow-up

**Effect of Acetazolamide on Visual Function in Patients with Idiopathic Intracranial Hypertension and Mild Visual Loss (IIHTT)**
JAMA 2014;311(16):1641-1651
**Methods**: RCT comparing low-sodium weight-reduction diet plus maximally tolerated dose of acetazolamide (up to 4 g/d) to diet alone in 165 patients with IIH and mild visual loss.
**Results**: Acetazolamide was superior to placebo with regards to perimetric mean deviation improvement (p=0.05), papilledema grade improvement (p<0.001), vision-related quality of life (p=0.003), and weight reduction (p<0.001).
**Conclusion**: Acetazolamide with low-sodium weight-reduction diet resulted in improvement in visual field function in patients with IIH and mild visual loss.

# Hydrocephalus

- for hydrocephalus in children, see *Pediatric Neurosurgery*, NS36

### Definition
- accumulation of excess CSF in the brain, functionally divided into obstructive and communicating
  - flow of CSF: produced by choroid plexus, lateral ventricles → foramen of Monroe → 3rd ventricle → cerebral/Sylvian aqueduct → 4th ventricle → foramina of Luschka (lateral) and Magendie (medial) → subarachnoid space where CSF is re-absorbed by arachnoid villi/granulations into dural venous sinuses

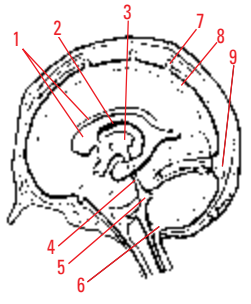
CSF production = CSF reabsorption = ~ 500 mL/d in normal adults
Normal CSF volume ~150 mL (50% spinal, 50% intracranial → 25 mL intraventricular, 50 mL subarachnoid)

### Classification

**Table 6. Classification of Hydrocephalus**

| Disorder | Definition | Etiology | Findings on CT/MRI |
|---|---|---|---|
| **Obstructive (Non-Communicating) Hydrocephalus** | CSF circulation blocked within ventricular system proximal to the arachnoid granulations | **Acquired**<br>**Aqueductal stenosis:** adhesions after infection, hemorrhage; gliosis, tumour (e.g. medulloblastoma)<br>**Intraventricular lesions**: tumours, e.g. 3rd ventricle colloid cyst, hematoma<br>Mass causing tentorial herniation causing aqueduct/4th ventricle compression<br>**Others:** neurosarcoidosis, abscess/granulomas, arachnoid cysts<br><br>**Congenital**<br>Primary aqueductal stenosis, Dandy-Walker malformation, Arnold-Chiari malformation, myelomeningocele, encephalocele (see *Pediatric Neurosurgery*, NS35) | Ventricular enlargement proximal to block (enlarged temporal horns, ballooning frontal and/or occipital horns, enlarged 3rd ± 4th ventricles)<br>Periventricular hypodensity/lucency (transependymal migration of CSF forced into extracellular space)<br>Sulcal effacement, reduced visibility of Sylvian and interhemispheric fissures |
| **Non-Obstructive (Communicating) Hydrocephalus** | Most commonly CSF absorption blocked at extraventricular site = arachnoid granulations, rarely CSF absorption is overwhelmed by increased production | Post-infectious (#1 cause) → meningitis, abscess, cysticercosis<br>Post-hemorrhagic (#2 cause) → SAH, IVH, traumatic<br>Leptomeningeal carcinomatosis – metastatic meningitis<br>Choroid plexus papilloma<br>Idiopathic → NPH | All ventricles dilated |
| **Normal Pressure Hydrocephalus (NPH)** | Persistent ventricular dilatation in the context of normal CSF pressure | Idiopathic (50%)<br>Others: SAH, meningitis, trauma, radiation-induced | Enlarged ventricles without increased prominence of cerebral sulci |
| **Hydrocephalus *Ex Vacuo*** | Ventricular enlargement resulting from atrophy of surrounding brain tissue | Normal aging<br>Degenerative dementias see Neurology, N22 (Alzheimer's, frontotemporal, Creutzfeldt-Jacob disease) | Enlarged ventricles and sulci<br>Cerebral atrophy |

### Etiology
- impaired CSF dynamics
  - obstruction of CSF flow
  - decreased CSF absorption
  - increased CSF production (rarely in choroid plexus papilloma – 0.4-1% of intracranial tumours)
- congenital and acquired causes




1. Lateral ventricles
2. Choroid plexus
3. Third ventricle
4. Cerebral aqueduct (of Sylvius)
5. Fourth ventricle
6. Foramina of Luschka and Magendie
7. Arachnoid granulations
8. Subarachnoid space
9. Superior sagittal sinus

© Kari Francis 2004

**Figure 8. The flow of CFS**

## Epidemiology
- estimated prevalence 1-1.5%; incidence of congenital hydrocephalus ~1-2/1000 live births

## Clinical Features
- acute hydrocephalus: signs and symptoms of acutely elevated ICP (see Table 3)
- chronic/gradual onset hydrocephalus: (wk to mo; i.e. NPH) presents with a classic triad (Hakim's Triad)
  - **A**taxia (magnetic gait) + apraxia (pressure of ventricle on lower extremity motor fibres → gait disturbance)
  - **I**ncontinence (pressure on cortical bowel/bladder centre)
  - **D**ementia (subcortical)

**Classic (Hakim's) Triad of NPH Progression**
"Wet, wacky, wobbly": Incontinence, dementia, ataxia

## Investigations
- imaging
  - CT/MRI findings (see Table 6)
  - ultrasound (through anterior fontanelle in infants): ventriculomegaly, size and location of lesions (e.g. IVH)
  - mantle radionuclide cisternography can test CSF flow and absorption rate (unreliable)
- ICP monitoring (e.g. LP, EVD) may be used to investigate NPH and test response to shunting (lumbar tap test)

**Important Features to Note on CT and MRI (± contrast enhancement)**
- Lesions (± edema, necrosis, hemorrhage)
- Midline shifts and herniations
- Effacement of ventricles and sulci (often ipsilateral), basal cisterns
- Single or multiple (multiple implies metastasis)

## Treatment
- EVD
- intermittent LPs for transient communicating hydrocephalus (SAH, IVH in premature infants)
- eliminating obstruction (i.e. excision of mass, posterior fossa decompression for Chiari Malformation)
- endoscopic
  - endoscopic third ventriculostomy (ETV) ± choroid plexus cauterization (for obstructive hydrocephalus)
  - endoscopic placement of aqueductal stent
- shunt
  - ventriculoperitoneal (VP): most common shunt
  - ventriculopleural (VPl)
  - ventriculoatrial (VA)
  - lumboperitoneal: for communicating hydrocephalus and pseudotumour cerebri

## Shunt Complications

**Table 7. Shunt Complications**

| Complication | Etiology | Clinical Features | Investigations |
|---|---|---|---|
| **Obstruction** (most common) Proximal Catheter Valve Distal Catheter | Obstruction by choroid plexus Buildup of proteinaceous accretions, blood, cells (inflammatory or tumour) Infection Disconnection or damage | Acute hydrocephalus signs and symptoms of increased ICP | "Shunt series" (plain x-rays of entire shunt that only rule-out disconnection, break, tip migration) CT Radionuclide "shuntogram" |
| **Infection** (3-6%) | *S. epidermidis* *S. aureus* *P. acnes* Gram-negative bacilli | Fever, N/V, anorexia, irritability Meningitis Peritonitis Signs and symptoms of shunt obstruction Shunt nephritis (VA shunt) | CBC Blood culture Tap shunt for CandS (LP usually NOT recommended) |
| **Overshunting** (10% over 6.5 yr) | Slit ventricle syndrome, collapse of ventricles leading to occlusion of shunt ports by ependymal lining | Chronic or recurring H/A often relieved when lying down | CT/MRI Slit-like ventricles on imaging |
| | Subdural hematoma Collapsing brain tears bridging veins (especially common in NPH patients) | Asymptomatic H/A, vomiting, somnolence | CT |
| | Secondary craniosynostosis (children): apposition and overlapping of the cranial sutures in an infant following decompression of hydrocephalus | Abnormal head shape | Clinical CT |
| **Seizures** (5.5% risk in 1st yr, 1.1% after 3rd yr) | Ventricular shunts only | | EEG |
| **Inguinal Hernia** (17% incidence with VP shunt inserted in infancy) ± skin breakdown over hardware | Increased intraperitoneal pressure/fluid results in hernia becoming apparent | Inguinal swelling, discomfort | U/S |

**Complications of Specific Hydrocephalus Treatments**
1. VP Shunt – intra-abdominal cysts, adhesions, ascites
2. VA Shunt – greater infection risk, septicemia, emboli
3. VPl Shunt – pleural effusion, hydrothorax, respiratory distress
4. LP Shunt – radiculopathy, CSF leaks, adhesions, arachnoiditis
5. ETV – 56% success rate, hypothalamic injury, traumatic basilar aneurysm

# CNS Tumours

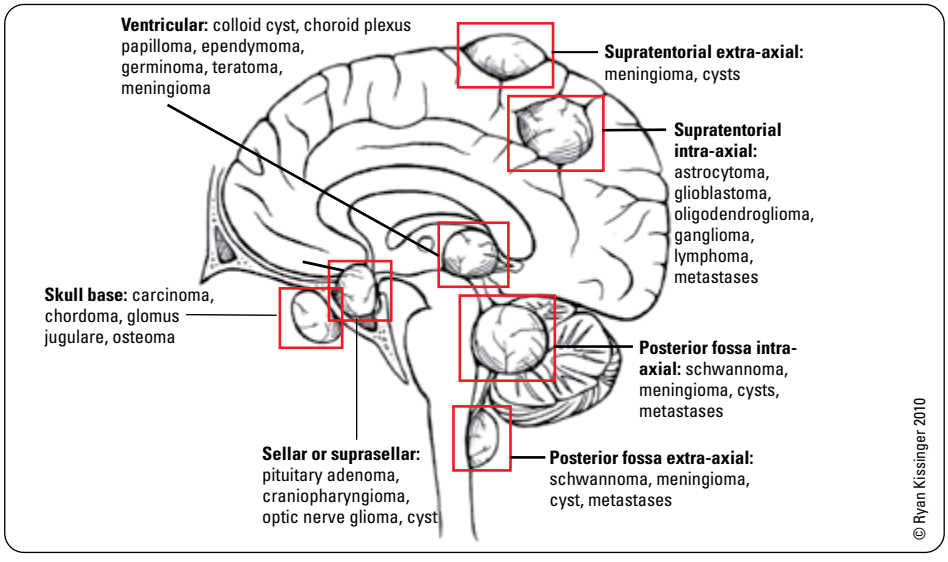



**Figure 9. Tumours of the CNS**

## Classification

- primary vs. metastatic (e.g. primary in breast, lung), intra-axial (parenchymal) vs. extra-axial, supratentorial vs. infratentorial, adult vs. pediatric
- benign: non-invasive, but can be devastating due to mass effect in fixed volume of skull (e.g. most meningiomas, WHO Grade I)
- malignant: implies rapid growth, invasiveness, possibly drop-metastases to spinal cord from a primary CNS tumour (rare)
- classification of nervous system tumours (* = most common). In 2007, the WHO Classification of CNS tumours was based solely on histology; an update was made in 2016 which bases the classification on a combination of histology (phenotype) and molecular genetics (genotype) for "integrated" diagnoses:
  - **neuroepithelial**
    - astrocytic tumours
      - oligoastrocytic tumours: oligoastrocytoma
      - neuronal and mixed neuronal-glial tumours: ganglion cell tumours, cerebral neurocytomas
      - embryonal tumours: medulloblastoma, PNET
      - other: pineal, ependymal, and choroid plexus tumours
  - **meningeal**: meningiomas*, mesenchymal, hemangioblastomas
  - **cranial and paraspinal nerves**: schwannoma, neurofibroma
  - **lymphomas and hematopoietic**: primary CNS lymphoma, plasmacytoma
  - **germ cell**: germinomas, teratomas, choriocarcinomas
  - **sellar region**: craniopharyngiomas, spindle cell oncocytoma, pituitary adenomas*
  - **cysts**: epidermoid/dermoid cysts, colloid cysts
  - **local extension**: chordomas, glomus jugulare tumours
  - **metastatic tumours**: lung*, breast*, melanoma

## Familial Syndromes Associated with CNS Tumours

- ataxia telangiectasia, Cowden syndrome, familial adenomatous polyposis, hereditary non-polyposis-related colorectal cancer, Li-Fraumeni Syndrome, Gorlin syndrome, neurofibromatosis Types 1 & 2, multiple endocrine neoplasia type 1, tuberous sclerosis complex, von Hippel-Lindau disease, and Turcot syndrome

## Investigations

- CT, MRI with contrast, stereotactic biopsy (tissue diagnosis and molecular markers for prognosis), metastatic workup, tumour markers (i.e. germ cell tumours)

## Treatment

- **conservative**: serial Hx, Px, imaging for slow growing/benign lesions
- **medical**: corticosteroids to reduce ICP, cytotoxic cerebral edema, pharmacologic (i.e. pituitary adenoma)
- **surgical**: total or partial excision (decompressive, palliative), shunt if hydrocephalus
- **radiotherapy**: conventional fractionated radiotherapy (XRT), stereotactic radiosurgery (SRS) (e.g. Gamma Knife®)
- **chemotherapy**: e.g. alkylating agents (i.e. temozolomide (GBM)*, vincristine, cyclophosphamide, etc.)

**DDx for Ring Enhancing Lesion on CT with Contrast**

**MAGICAL DR**
**M**etastases*
**A**bscess*
**G**lioblastoma (high grade astrocytoma)*
**I**nfarct
**C**ontusion
**A**IDS (toxoplasmosis)
**L**ymphoma
**D**emyelination
**R**esolving hematoma, **R**adiation Necrosis
(*3 most common diagnoses)

**Ring Enhancing Lesions in Patients with HIV**
DDx: Toxoplasmosis or CNS Lymphoma
Tx: Pyrimethamine and Sulfadiazine; later brain biopsy if no resolution with antimicrobial
Primary CNS lymphoma reported in 6-20% of HIV infected patients

**Primary Brain Tumours**
Rarely undergo metastasis
Adults = mostly supratentorial
Children = mostly infratentorial

New onset communicating hydrocephalus in a patient with cancer should raise the suspicion of leptomeningeal carcinomatosis

**Table 8. Tumour Location: Etiology and Clinical Feature**

| | Supratentorial | Infratentorial (Posterior Fossa) |
|---|---|---|
| **Epidemiology** | | |
| **Age <15 yr** Incidence: 2-5/100,000/yr<br>60% infratentorial | Astrocytoma (all grades) (50%)<br>Craniopharyngioma (2-5%)<br>Others: pineal region tumours, choroid plexus tumours, ganglioglioma, DNET | Medulloblastoma (15-20%)<br>Cerebellar astrocytoma (15%)<br>Ependymoma (9%)<br>Brainstem astrocytoma |
| **Age >15 yr**<br>80% supratentorial | High grade astrocytoma (12-15%, e.g. GBM)<br>Metastasis (15-30%, includes infratentorial)<br>Meningioma (15-20%)<br>Low grade astrocytoma (8%)<br>Pituitary adenoma (5-8%)<br>Oligodendroglioma (5%)<br>Other: colloid cyst, CNS lymphoma, dermoid/epidermoid cysts | Metastasis<br>Acoustic neuroma (schwannoma) (5-10%)<br>Hemangioblastoma (2%)<br>Meningioma |
| **Clinical Feature** | | |
| **Shared Features** (from elevated ICP) | **H/A**: usually worse in AM and made worse with straining, coughing<br>**N/V**<br>**Papilledema**<br>**Diplopia** - CN VI palsy | |
| **Distinguishing Features** | **Seizure**: commonly the first symptom<br>Progressive neurological deficits (70%)<br>Frontal lobe: hemiparesis, dysphasia, personality changes, cognitive changes<br>Temporal lobe: auditory/olfactory hallucinations, memory deficits, contralateral superior quadrantanopsia<br>**Mental Status Change**: depression, apathy, confusion, lethargy<br>**"Tumour TIA"** (transient ischemic attack) stroke like symptoms caused by<br>a) occlusion of vessel by tumour cells<br>b) hemorrhage<br>c) 2° to "steal phenomenon" - blood is shunted from ischemic regions to non-ischemic regions<br>Endocrine disturbance - with pituitary tumours (see Endocrinology, E20) | **Brainstem involvement**: cranial nerve deficits and long tract signs<br>**N/V**: compression on vagal nucleus/area postrema<br>**Diplopia**: direct compression CN VI<br>**Vertigo**<br>**Nystagmus**<br>**Truncal ataxia + titubation**: cerebellar vermis lesions<br>**Limb ataxia, dysmetria, intention tremor:** cerebellar hemisphere lesions<br>**Obstructive hydrocephalus** more common than supratentorial lesions |

# Metastatic Tumours

## Brain Metastasis

- most common intra-cranial tumour in adults (~50% of all brain tumours)
- afflict ~25% of patients with any cancer
- hematogenous spread most common
- 80% are hemispheric, often at grey-white matter junction or temporal-parietal-occipital lobe junction
  - likely emboli spreading to terminal MCA branches

## Investigations

- identify primary tumour
  - full metastatic workup (CXR, CT chest/abdo, abdominal U/S, nuclear medicine scan/PET, mammogram)
- CT with contrast → round, well-circumscribed, often ring enhancing, ++ edema, often multiple
- contrast-enhanced MRI more sensitive, especially for posterior fossa
- consider biopsy in unusual cases or if no primary tumour identified

## Treatment

- medical
  - phenytoin (or levetiracetam) for seizure prophylaxis if patient presents with seizure
  - dexamethasone to reduce edema given with ranitidine
  - chemotherapy (e.g. small cell lung cancer), but difficult delivery across BBB
- radiation
  - SRS (highly focused fraction of radiation targeted to tumour): for discrete, deep-seated/inoperable tumours
  - multiple lesions: use WBRT (upwards of 10 lesions); consider SRS if <3 lesions
  - post-operative adjuvant RT consideration
  - emerging evidence supports avoidance of whole brain radiation and use of focal radiation to spare cognitive functions (refer to Brown et al., 2016)
- surgical
  - single/solitary lesions: surgical resection and radiation in carefully selected patients

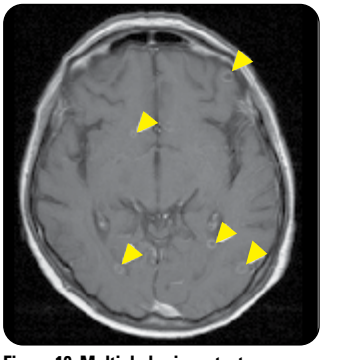


**Figure 10. Multiple brain metastases** (see arrows)

**Most Common Cancers that Metastasize to the CNS**

| Site of Primary | Frequency of CNS metastasize |
|---|---|
| **Lung** | 44% |
| **Breast** | 10% |
| **Kidney (RCC)*** | 7% |
| **GI** | 6% |
| **Melanoma** | 3% |

*RCC=renal cell carcinoma

### Prognosis
- median survival without treatment once symptomatic is ~1 mo, with optimal treatment 6-9 mo. The disease-specific Graded Prognostic Assessment (Ds-GPA) is a useful prognostic index. Prognosis varies depending on primary tumour type and extent of systemic tumour burden

## Astrocytoma
- most common primary intra-axial brain tumour, common in 4th-6th decades

**Table 9. World Health Organization Astrocytoma Grading System**

| | Typical CT/MRI Findings | Survival |
|---|---|---|
| **I – Pilocytic astrocytoma** | ± mass effect, ± enhancement | >10 yr, cure if gross total resection |
| **II – Low grade/diffuse*** | Mass effect, no enhancement | 5 yr |
| **III – Anaplastic*** | Complex enhancement | 1.5-2 yr |
| **IV – Glioblastoma multiforme (GBM)** | Necrosis (ring enhancement) | 12 mo, 10% at 2 yr |

*IDH mutant WHO Gr II/III tumours have a better overall prognosis than IDH wild-type; following IDH stratification, the chromosomal 1p/19q codeletion has prognostic value in IDH mutated grade II–III gliomas after adjustment for tumour proliferation, age, and adjuvant treatment

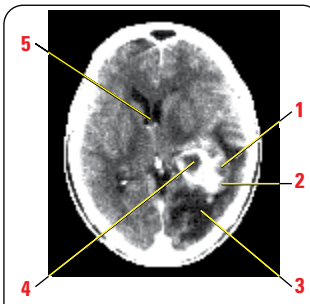
### Clinical Features
- sites: cerebral hemispheres >> cerebellum, brainstem, spinal cord
- symptoms: recent onset of new/worsening H/A, N/V, seizure, ± focal deficits or symptoms of increased ICP

### Investigations
- CT/MRI with contrast: variable appearance depending on grade
  - hypodense on CT, hypointense on T1 MRI, hyperintense on T2 MRI
  - low grade: most do not enhance and have calcification on CT
  - high grade: most enhance with CT contrast dye/gadolinium, possibly with central necrosis (especially if IDH wildtype)
  - histology during surgical resection or biopsy

### Treatment
- **low grade diffuse astrocytoma**
  - close follow-up, radiation, chemotherapy, and surgery all valid options
  - de-differentiation to more malignant grade; typically occurs faster when diagnosed after age 45
  - surgery: maximal safe resection, not curative, trend towards better outcomes, provides tissue sample for histologic/molecular characterization
  - radiotherapy alone or post-operative prolongs survival (retrospective evidence)
  - chemotherapy: usually reserved for tumour progression
- **high grade astrocytomas** (anaplastic astrocytoma and GBM)
  - goal is to prolong "quality" survival
  - **surgery**
    - gross total resection: maximal safe resection + fractionated radiation with 2 cm margin + concomitant and adjuvant temozolomide
      - except: nearing end-of-life; or extensive brainstem, bilateral, or dominant lobe GBM involvement
    - awake craniotomy for tumours in 'eloquent' regions (e.g. speech and language regions or near motor strip)
    - stereotactic biopsy if resection not possible, followed by fractioned radiation with 2 cm margin
  - **expectant** (based on functional impairment – Karnofsky score <70; patient's/family's wishes)
  - **chemotherapy**: ~20% response rate, temozolomide (agent of choice); better response to temozolomide predicted by MGMT gene hypermethylation
- **multiple gliomas**: WBRT ± chemotherapy

## Meningioma
- most common ***primary*** intracranial tumour, arising from arachnoid membrane
- often calcified, may cause hyperostosis of adjacent bone (detectable on imaging)
- classically see Psammoma bodies ("meningocytic whorls") on histology
- location: 70% occur along the parasagittal convexity, falx cerebri, and sphenoid bone; other locations: tuberculum sellae, foramen magnum, olfactory groove, and CP angle

### Clinical Features
- middle aged, slight female predominance (M:F = 1:1.8), high progesterone receptors (increase in size with pregnancy)
- many are asymptomatic and can be an incidental finding; when symptoms occur focal neurologic deficits specific to location, ± seizures, symptoms of increased ICP
- molecular changes: between 40-80% of meningiomas contain mutations in chromosome 22 (involved in suppressing tumour growth); some have extra copies of PDGFR and EGFR; some are associated with mutations in the NF2 gene

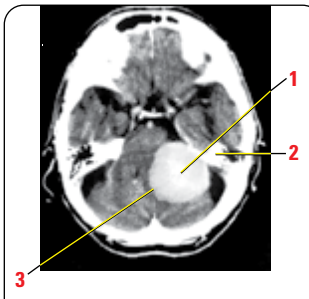


1. Heterogenous contrast enhancement
2. Ill-defined borders (infiltrative)
3. Peritumoural edema
4. Central necrosis
5. Compression of ventricles, midline shift

**Figure 11. High grade astrocytoma on CT**

**Comparison of a Strategy Favouring Early Surgical Resection vs. a Strategy Favouring Watchful Waiting in Low-Grade Gliomas**
JAMA 2012; 308(18): 1881-8
**Purpose**: To examine "watchful waiting" vs. early surgical resection of low grade gliomas.
**Study**: A population-based parallel cohort study was undertaken between two hospitals that each favoured different management approaches for low grade gliomas (biopsy and watchful waiting vs. early surgical resection).
**Results**: 66 patients were included from the watchful waiting hospital and 87 patients from the early resection centre. Median follow-up was 7.0 and 7.1 years at each centre. The two groups were equivalent in terms of baseline parameters. Overall, survival was significantly better with early surgical resection (watchful waiting: median survival of 5.9 years 95% CI, 4.5-7.3 vs. early resection: median survival was not reached due to prolonged length of life, p<0.01).
**Conclusions**: Early surgical resection of low grade-gliomas is associated with better overall survival as compared to watchful waiting.

**Bevacizumab Plus Radiotherapy-Temozolamide for Newly Diagnosed Glioblastoma**
NEJM 2014;370:709-722
**Purpose**: To evaluate the effect of combined bevacizumab and radiotherapy-temozolamide in the treatment of newly diagnosed glioblastoma.
**Study**: Patients with supratentorial glioblastoma randomly assigned to receive intravenous bevacizumab or placebo plus radiotherapy and oral temozolamide for 30 wk total in cycles, followed by bevacizumab or placebo monotherapy. Outcomes were progression-free survival and overall survival.
**Results**: 458 patients in bevacizumab group, 463 patients in placebo. The median progression-free survival was longer in the bevacizumab group compared with placebo (10.6 mo vs. 6.2 mo, HR 0.64, 95% CI 0.55-0.74), although overall survival did not differ significantly between groups (HR 0.88, 95% CI 0.76-1.02). Baseline health-related QOL and performance status were maintained longer in the bevacizumab group although there was a higher frequency of adverse events.
**Conclusions**: The addition of bevacizumab to radiotherapy-temozolamide improves progression-free survival but not overall survival in patients with glioblastoma.



1. Homogenous contrast enhancement
2. Dural attachment
3. Distinct margins

**Figure 12. Meningioma on CT**

### Investigations
- **CT with contrast**: homogeneous, densely enhancing, along dural border ("dural tail"), well circumscribed, usually solitary (10% multiple, likely with loss of NF2 gene/22q12 deletion)
- **MRI with contrast**: characterization of mass and provides a better assessment of the patency of dural venous sinuses
- **angiography**
  - most are supplied by external carotid feeders (meningeal vessels)
  - can assess venous sinus involvement, "tumour blush" commonly seen (prolonged contrast image)

### Treatment
- **conservative management**: asymptomatic and/or non-progressive on CT/MRI – serial monitoring for interval growth changes
- **surgery**: curative if complete resection and indicated when symptomatic and/or documented growth on serial CT/MRI
- **endovascular**: embolization for highly vascularized, likely bloody, tumours to facilitate surgery
- **radiation**: SRS may be an option for lesions <3 cm partially occluding the superior sagittal sinus; SRS or XRT for non-resectable, recurrent atypical/malignant meningiomas

### Prognosis
- 5 yr survival is 7-25% for Grade I, 30-50% for Grade II, and 50-94% for Grade III
- depends on extent of resection
- Simpson's classification: degree of surgical resection completeness with symptomatic recurrence

**WHO Classification of Meningioma (by histology)**
Grade 1: low risk of recurrence
Grade 2: intermediate risk of recurrence
Grade 3: high risk of recurrence

**Recommendations for Management of Meningiomas**
Lancet Oncol 2016;17(9):e383-91
European Association of Neuro-Oncology assessed available literature and rated scientific evidence and graded recommendation levels.
Despite high frequency of meningiomas, evidence for diagnosis and treatment recommendation are low. Prospective studies to generate new evidence is required.
Key recommendations include:
1. First standard therapy is gross total surgical resection (including involved dura).
2. Alternative treatments include radiosurgery for small tumours and fractionated radiotherapy in large/previously treated tumours.
3. New treatment concepts combining surgery and radiosurgery/fractionated radiotherapy to treat complete tumour volume are being developed.
4. Although pharmacological treatments are still experimental, antiangiogenic drugs, peptide receptor radionuclide therapy, and targeted agents are candidates for future pharmacological approaches to treat refractory meningioma of all WHO grades.

## Vestibular Schwannoma (Acoustic Neuroma)

- slow-growing (60% show no growth over 1 yr; average rate for growing tumours 1-2 mm/yr), benign posterior fossa tumour (8-10% of tumours)
- arises from vestibular nerve of CN VIII in internal auditory canal, expanding into bony canal and cerebello-pontine angle (CPA)
- if bilateral, diagnostic of NF2
- epidemiology: 1.5/100,000; all age groups affected, peaks at 4th-6th decades

### Clinical Features
- **early clinical triad**: (tumour <2 cm) unilateral progressive hearing loss 98%, tinnitus, and disequilibrium (compression of CN VIII)
- **later clinical features**
  - tumour usually >2 cm: otalgia, facial numbness + weakness, changes to taste (due to CN V and VII compression, respectively)
  - tumour usually >4 cm: ataxia, H/A, N/V, diplopia, cerebellar signs (due to brainstem compression; ± obstructive hydrocephalus)

Progressive unilateral or asymmetrical sensorineural hearing loss = acoustic neuroma until proven otherwise

### Investigations
- MRI with gadolinium or T2 FIESTA sequence (>98% sensitive/specific); CT with contrast 2nd choice
- audiogram, brainstem auditory evoked potentials, caloric tests

### Treatment
- expectant: serial imaging (CT/MRI q6mo) and audiometry if tumour is small, hearing is still preserved, high perioperative risk, or elderly patient
- radiation: SRS or XRT
- surgery: if lesion >3 cm, brainstem compression, edema, hydrocephalus
- curable if complete resection (almost always possible)
- operative complications: CSF leak, meningitis, required shunt; CN V, VII, VIII dysfunction (proportional to tumour size; only significant CNVIII disability if bilateral)
- implications for testing of family members of NF2 mutation carrier

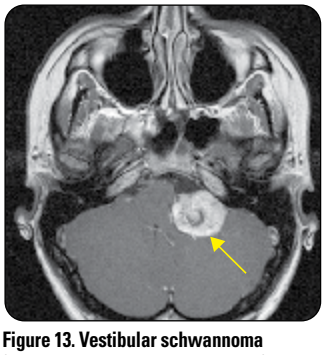


**Figure 13. Vestibular schwannoma** (tumour in cerebello-pontine angle)

## Pituitary Adenoma

- primarily from anterior pituitary, 3rd-4th decades, M=F, associated with MEN-1 syndrome
- incidence in autopsy studies approximately 20%
- **classification**
  - microadenoma <1 cm; macroadenoma ≥1 cm
  - endocrine active (functional/secretory) vs. inactive (non-functional)
  - most common functional: prolactinomas, adrenocorticotropic, growth-hormone (GH) producing
  - differential diagnosis: parasellar tumours (e.g. craniopharyngioma, tuberculum sellae meningioma), carotid aneurysm

**Go Look For The Adenoma Please – GH, LH, FSH, TSH, ACTH, Prolactin**
A compressive adenoma in the pituitary will impair hormone production in this order (i.e. GH-secreting cells are most sensitive to compression)

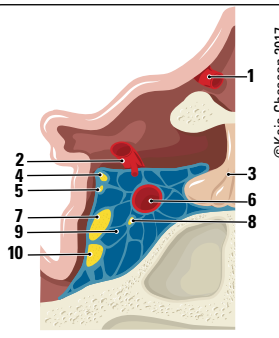
### Clinical Features
- mass effects
- H/A
- bitemporal hemianopsia (compression of optic chiasm); hydrocephalus (3rd ventricle compression)
- invasive adenomas: CN III, IV, V1, V2, VI palsy (cavernous sinus compression); proptosis and chemosis (cavernous sinus occlusion)
- endocrine effects (see Endocrinology, E20)
  - hyperprolactinemia (prolactinoma): infertility, amenorrhea, galactorrhea, decreased libido

- ACTH production: Cushing's disease, hyperpigmentation
- GH production: acromegaly/gigantism
- panhypopituitarism: due to compression of pituitary (hypothyroidism, hypoadrenalism, hypogonadism)
- DI – rare, except in apoplexy

- pituitary apoplexy (sudden expansion of mass due to hemorrhage or necrosis)
  - abrupt onset H/A, visual disturbances, ophthalmoplegia, reduced mental status, panhypopituitarism and DI
  - CSF rhinorrhea and seizures (rare)
  - signs and symptoms of SAH (rare)

### Investigations
- formal visual fields, CN testing
- endocrine tests (prolactin level, TSH, 8 AM cortisol, fasting glucose, FSH/LH, IGF-1), electrolytes, urine electrolytes, and osmolarity
- imaging (MRI with and without contrast)

### Treatment
- medical
  - for apoplexy: rapid corticosteroid administration ± surgical decompression
  - for prolactinoma: dopamine agonists (e.g. bromocriptine)
  - for Cushing's: serotonin antagonist (cyproheptadine), inhibition of cortisol production (ketoconazole)
  - for acromegaly: somatostatin analogue (octreotide) ± bromocriptine
  - endocrine replacement therapy
- surgical
  - endoscopic trans-sphenoidal, trans-ethmoidal, and less commonly trans-cranial approaches (i.e. for significant suprasellar extension)
- post-operative concerns: DI, adrenal insufficiency (AI), CSF leak
  - DI and AI: AM cortisol, serum sodium and osmolality, urine output and specific gravity (treatment - AI: glucocorticoids; DI: desmopressin/DDAVP)
  - CSF rhinorrhea: test for β transferrin




1. Anterior cerebral artery
2. Internal carotid artery (cerebral part)
3. Pituitary gland
4. Oculomotor nerve
5. Trochlear nerve
6. Internal carotic artery (cavernous part)
7. Ophthalmic nerve
8. Abducent nerve
9. Cavernous sinus
10. Maxillary nerve

**Figure 14. Cavernous sinus**

### Genetic Associations
- Sellar masses have known associations with several classic oncogene mutations, including:
  - *MEN1*: loss-of-function mutations are common
  - Gs-alpha: activating mutations found in ~40% of somatotroph adenomas
  - AIP: mutations associated with familial pituitary adenomas

# Cerebral Abscess

### Definition
- pus in brain substance, surrounded by tissue reaction (capsule formation)

### Etiology
- modes of spread: 10-60% of patients have no cause identified
- pathogens
  - *Streptococcus* (most common), often anaerobic or microaerophilic
  - *Staphylococcus* (penetrating injury)
  - Gram-negatives, anaerobes (*Bacteroides, Fusobacterium*)
  - in neonates: *Proteus* and *Citrobacter* (exclusively)
  - immunocompromised: fungi and protozoa (*Toxoplasma, Nocardia, Candida albicans, Listeria monocytogenes, Mycobacterium*, and *Aspergillus*)

### Sources of Pus/Infection
- four routes of microbial access to CNS
  1. hematogenous spread: arterial and retrograde venous
     - adults: chest is #1 source (lung abscess, bronchiectasis, empyema)
     - children: congenital cyanotic heart disease with R-to-L shunt
     - immunosuppression (AIDS – toxoplasmosis)
  2. direct implantation (dural disruption)
     - trauma
     - iatrogenic (e.g. following LP, post-operative)
     - congenital defect (e.g. dermal sinus)
  3. contiguous spread (adjacent infection): from air sinus, naso/oropharynx, surgical site (e.g. otitis media, mastoiditis, sinusitis, osteomyelitis, dental abscess)
  4. spread from PNS (e.g. viruses: rabies, herpes zoster)
- common examples
  - epidural abscess: in cranial and spinal epidural space, associated with osteomyelitis
    - treatment: immediate drainage and antibiotics, surgical emergency if cord compression
  - subdural empyema: bacterial/fungal infection, due to contiguous spread from bone or air sinus, progresses rapidly
    - treatment: surgical drainage and antibiotics, 20% mortality
  - meningitis, encephalitis (see Infectious Diseases, ID15)
  - cerebral abscess

### Risk Factors
- lung abnormalities (infection, AVFs; especially Osler-Weber-Rendu syndrome [i.e. hereditary hemorrhagic telengiectasia])
- congenital coronary heart disease: R-to-L shunt bypasses pulmonary filtration of micro-organisms
- bacterial endocarditis
- penetrating head trauma
- immunosuppression (e.g. AIDS)
- dental abscess, poor dentition

### Clinical Features
- focal neurological signs and symptoms
  - H/A, decreased LOC; hemiparesis and seizures in 50%
- mass effect, increased ICP and sequelae (cranial enlargement in children)
- hemiparesis and seizures in 50%
- ± signs and symptoms of systemic infection (low-grade fever, leukocytosis)

### Complications
- with abscess rupture: ventriculitis, meningitis, venous sinus thrombosis
- CSF obstruction
- transtentorial herniation

### Investigations
- CT scan often first test in emergency department
- MRI
  - imaging of choice
  - apparent diffusion coefficient (ADC) used to differentiate abscess (black) from tumour (white)
- WBC/ESR may be normal, blood cultures rarely helpful and LP contraindicated if large mass
- CSF: non-specific (high ICP, high WBC, high protein, normal carbohydrate), rarely helpful, usually negative culture

### Treatment
- aspiration ± excision and send for Gram stain, acid fast bacillus (AFB), C&S, fungal culture
- excision preferable if location suitable
- antibiotics
  - empirically: vancomycin + ceftriaxone + metronidazole or chloramphenicol or rifampin (6-8 wk therapy)
  - revise antibiotics when C&S known
- anti-convulsants (1-2 yr)
- follow-up CT is critical (do weekly initially, more frequent if condition deteriorates)

### Prognosis
- mortality with appropriate therapy ~10%, permanent deficits in ~50%

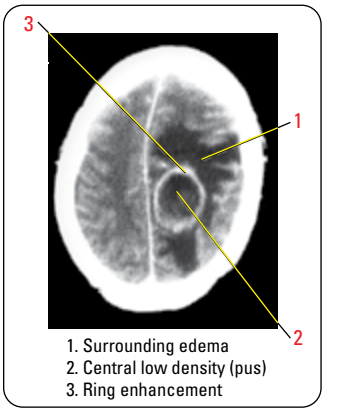



**Figure 15. Cerebral abscess on CT**

**Recommendations for Duration of Antibiotic Therapy for Brain Abscesses**
Int J Infect Dis 2010;14 Suppl 4:S79-92
**Summary:**
1. Prudent period of 4-6 weeks of antibiotic therapy for surgically treated abscesses.
2. 6-8 weeks of IV treatment for abscesses treated medically only.
3. 6-8 weeks of IV treatment for multiple abscesses when larger ones are treated surgically.
**Methods**: Systematic literature search using MEDLINE database for studies during 1988-2008 to methodologically evaluate all studies pertaining to brain abscess.
**Results**: Several recommendations were made by extracting evidence; for duration of antibiotic therapy, it was noted that IV antibiotic therapies were usually ≥4 weeks. No studies have evaluated the duration of antibiotic therapy on outcome. Without evidence to safely evaluate endovenous therapy time, authors agreed with British Society for Antimicrobial Chemotherapy recommendations (see summary).

# Blood

**Table 10. Comparison of Epidemiology and Etiology of Intracranial Bleeds**

| Types of Hematoma/ Hemorrhage | Etiology | Epidemiology | Clinical Features | CT Features | Treatment | Prognosis |
|---|---|---|---|---|---|---|
| **Epidural Hematoma** | Skull fracture causing middle meningeal bleed | M>F (4:1), associated with trauma | Lucid interval before LOC | Hyperdense lenticular mass with sharp margins, usually limited by suture lines | Craniotomy | Good with prompt management (Note: respiratory arrest can occur from uncal herniation) |
| **Acute SDH** | Ruptured subarachnoid bridging vessels | Age >50, associated with trauma | No lucid interval, hemiparesis, pupillary changes | Hyperdense crescentic mass, crossing suture lines | Craniotomy if bleed >1 cm thick | Poor |
| **Chronic SDH** | Ruptured subarachnoid bridging vessels | Age >50, EtOH abusers, anticoagulated | Often asymptomatic, minor H/A, confusion, signs of increased ICP, llight-headedness | Hypodense crescentic mass, crossing suture lines | Burr hole to drain; craniotomy if recurs | Good |
| **SAH** | Trauma, spontaneous (aneurysms, idio-pathic, AVM) | Age 55-60, 20% cases under age 45 | Sudden onset thunderclap H/A, signs of increased ICP | Hyperdense blood in cisterns/fissures (sensitivity decreases over time) | Conservative: NPO, IV NS, ECG, Foley, BP 120-150, vasospasm prophylaxis (nimodipine); open vs. endovascular surgery to repair if rebleed | Poor: 50% mortality; 30% of survivors have moderate to severe disability |
| **ICH** | HTN, vascular abnormality, tumours, infections, coagulopathy | Age >55, male, drug use (cocaine, EtOH, amphetamine) | TIA-like symptoms, signs of increased ICP | Hyperdense intra-parenchymal collection | Medical: decrease BP, control ICP<br>Surgical: craniotomy | Poor: 44% mortality due to cerebral herniation |

**CT Density and MRI Appearance of Blood**

| Time | CT | MRI T1 | MRI T2 |
|---|---|---|---|
| Acute (<72 h) | Hyper. | Grey | Black |
| Subacute (<3 wk) | Iso. | White | White |
| Chronic (>3 wk) | Hypo. | Black | Black |

MRI-T1: "**G**eorge **W**ashington **B**ridge"
MRI-T2: "Oreo" cookie – **B**lack/**W**hite/**B**lack

# Extradural ("Epidural") Hematoma

## Etiology
- temporal-parietal skull fracture: 85% are due to ruptured middle meningeal artery; remainder of cases are due to bleeding from middle meningeal vein, dural sinus, or bone/diploic veins

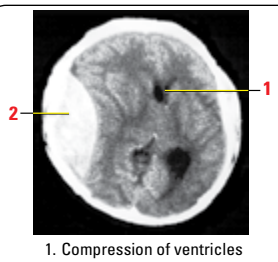
## Epidemiology
- young adult, M>F = 4:1; rare before age 2 or after age 60
- 1-4% of traumatic head injuries

## Clinical Features
- classic sequence (seen in <30%): post-traumatic reduced LOC, a lucid interval of several hours, then obtundation, hemiparesis, ipsilateral pupillary dilatation, and coma
- signs and symptoms depend on severity but can include H/A, N/V, amnesia, altered LOC, aphasia, seizures, HTN, and respiratory distress
- deterioration can take hours to days

## Investigations
- CT without contrast: "lenticular-shaped" usually limited by suture lines but not limited by dural attachments (not visible on initial CT in 8% of cases)

## Treatment
- admission, close neurological observation with serial CT indicated if all of the following are present
  - small volume clot (<30 mL), clot thickness <15 mm, minimal midline shift (MLS <5 mm), GCS >8, no focal deficit
- otherwise, urgent craniotomy to evacuate clot, follow-up CT
- patients with initial EDH >10 mL on CT within 2 h or EDH in temporoparietal region are more likely to develop epidural hematoma enlargement and require close CT follow-up at 5-6 h post impact
- mannitol pre-operative if elevated ICP or signs of brain herniation
- reverse anticoagulation if on warfarin

## Prognosis
- good with prompt management, as the brain is often not damaged
- worse prognosis if bilateral Babinski or decerebration pre-operative
- death is usually due to respiratory arrest from uncal herniation (injury to the midbrain)




1. Compression of ventricles (midline shift)
2. Blood

**Figure 16. Extradural hematoma on CT**

**Poor Prognostic Indicators for Epidural Hematoma**
- Older age
- Low GCS on admission
- Pupillary abnormalities (especially non-reactive)
- Longer delay in obtaining surgery (if needed)
- Post-operative elevated ICP

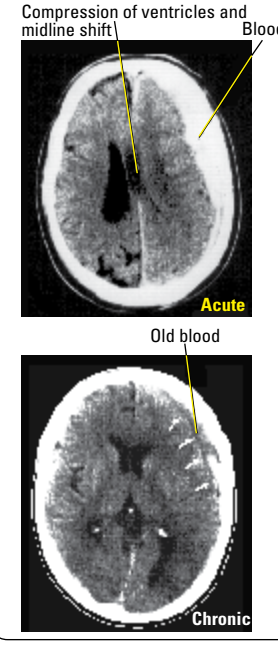



**Figure 17. Subdural hematoma on CT**

# Subdural Hematoma

**Table 11. Comparison of Epidemiology and Etiology of Acute and Chronic SDH**

| | Acute SDH | Chronic SDH |
|---|---|---|
| **Time Course** | 1-2 d after bleeding onset | ≥15 d after bleeding onset |
| **Etiology** | Rupture of vessels that bridge the subarachnoid space (e.g. cortical artery, large vein, venous sinus) or cerebral laceration | Many start out as acute SDH<br>Blood within the subdural space evokes an inflammatory response:<br>Fibroblast invasion of clot and formation of neomembranes within days → growth of neocapillaries → fibrinolysis and liquefaction of blood clot (forming a hygroma)<br>Course is determined by the balance of rebleeding from neomembranes and resorption of fluid |
| **Risk Factors** | Trauma, acceleration-deceleration injury, anticoagulants, alcohol, cerebral atrophy, infant head trauma | Older, alcoholics, patients with CSF shunts, anticoagulants, coagulopathies |
| **Clinical Features** | Signs and symptoms can include: altered LOC, pupillary irregularity, hemiparesis<br>Up to 50% of patients can present with coma from the time of injury | Often due to minor injuries or no history of injury<br>May present with minor H/A, confusion, language difficulties, TIA-like symptoms, symptoms of raised ICP ± seizures, progressive dementia, gait problem, light-headedness<br>Presents with global rather than focal deficits, such as disturbance of consciousness; "the great imitator" of dementia, tumours |
| **Investigations** | CT: Hyperdense concave "crescentic" mass, crossing suture lines | CT: hypodense (liquefied clot), crescentic mass |
| **Treatment** | Indications for craniotomy:<br>- if clinically symptomatic, hematoma >1 cm thick, MLS >5 mm, GCS decreased by >2 from time of injury to hospital admission, or ICP persistently >20 mmHg (optimal if surgery <4 h from onset)<br>Otherwise observe with serial imaging if stable or improving | Seizure prophylaxis only if post-traumatic seizure<br>Reverse coagulopathies<br>Burr hole drainage of liquefied clot indicated if symptomatic or thickness >1 cm; craniotomy if recurs more than twice |
| **Prognosis** | Poor overall since the brain parenchyma is often injured (mortality range is 50-90%, due largely to underlying brain injury)<br>Prognostic factors: initial GCS and neurological status, post-operative ICP | Good overall as brain usually undamaged, but may require repeat drainage |

**Use of Drains Vs. No Drains After Burr-Hole Evacuation For Treatment of Chronic Subdural Hematoma**
Cochrane Database Syst Rev. 2016;(8):CD011402
**Summary**:
1. Some evidence that post-operative drainage is effective in reducing the symptomatic recurrence of chronic subdural hematoma
2. The effect of drainage on the occurrence of surgical complications, mortality, and poor functional outcomes is uncertain due to low quality evidence
3. No strong evidence of increase in complications when drains are used

**Methods**: Comprehensive search strategy databases extracting 9 RCTs (n=968) comparing external subdural drains with no drains after burr-hole evacuation for treatment of chronic subdural hematoma.
**Results**: Significant reduction in the risk of recurrence with subdural drains (RR 0.45, 95% CI 0.32-0.61), no strong evidence of increase in complications (RR 0.78, 95% CI 0.77-1.72), mortality (RR 0.78, 95% CI–0.45-1.33), poor functional outcome (RR 0.68, 95% CI 0.44-1.05).

# Cerebrovascular Disease

**Cerebrovascular disease may be divided into two general categories:**

### Ischemic Cerebral Infarction (80% of disease)
- includes embolism, thrombosis of intracerebral arteries, vasculitis, hypercoagulability, etc. (see Neurology, N48)

### Intracranial Hemorrhage (20% of disease)
- includes SAH, spontaneous ICH, IVH
- may occur due to ruptured intracranial aneurysms

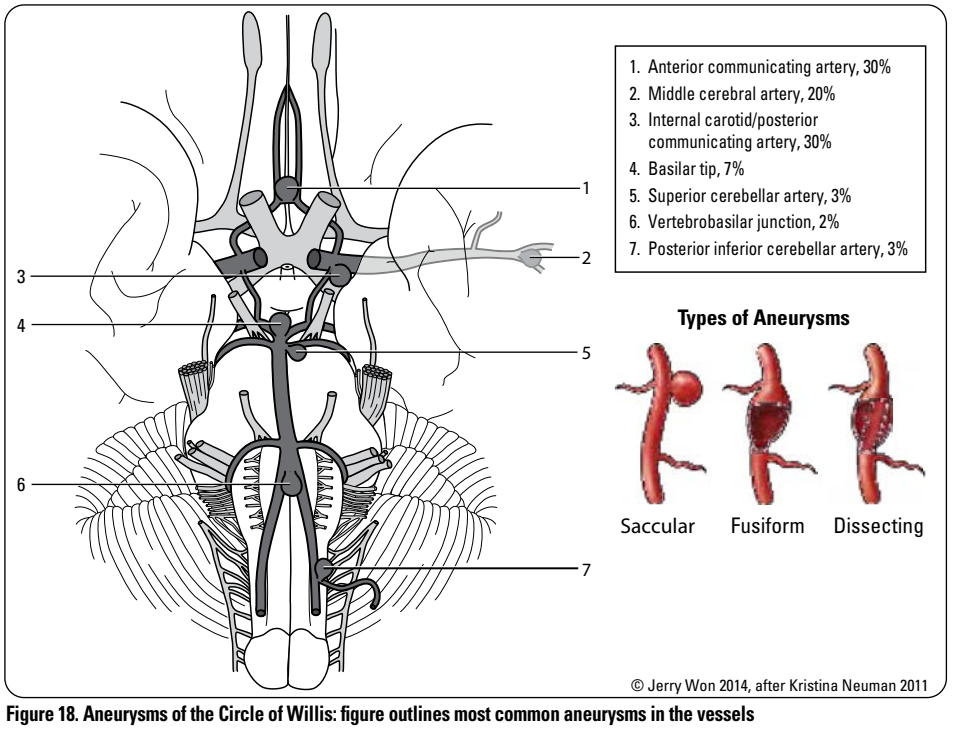



**Figure 18. Aneurysms of the Circle of Willis: figure outlines most common aneurysms in the vessels**

**Hemicraniectomy in Older Patients with Extensive Middle-Cerebral-Artery Stroke**
NEJM 2014;370:1091-1100
**Purpose**: To determine if early decompressive hemicraniectomy reduces mortality among patients >60 yr.
**Study**: 112 patients >60 yr (median age 70 yr) with malignant MCA infarction randomly assigned to conservative ICU treatment versus hemicraniectomy. Endpoint was survival without severe disability (modified Rankin scale score 0-4).
**Results**: The proportion of patients who survived without severe disability was 38% in the hemicraniectomy group and 18% in the control group (OR 2.91, 95% CI 1.06-7.49). Modified Rankin scale scores in hemicraniectomy versus control group in terms of percentages of patients: 0-2 (0%, 0%), 3 or moderate disability (7%, 3%), 4 or moderate severe disability (32%, 15%), 5 or severe disability (28%, 13%) and 6 or death (33%, 70%). Infections were more frequent in the hemicraniectomy group and herniation more frequent in the control group.
**Conclusions**: Hemicraniectomy increased survival without severe disability among patients >60 yr with a malignant MCA infarction.

# Subarachnoid Hemorrhage

### Definition
- bleeding into subarachnoid space (intracranial vessel between arachnoid and pia)

### Etiology
- trauma (most common)
- spontaneous
  - ruptured aneurysms (75-80%)
  - idiopathic (14-22%)
  - AVMs (4-5%)
- coagulopathies (iatrogenic or primary), vasculitides, tumours, cerebral artery dissections (<5%)

### Epidemiology
- ~10-28/100,000 population/yr
- peak age 55-60, 20% of cases occur under age 45

### Risk Factors
- HTN
- pregnancy/parturition in patients with pre-existing AVMs, eclampsia
- oral contraceptive pill
- substance abuse (cigarette smoking, cocaine, alcohol)
- conditions associated with high incidence of aneurysms (see *Intracranial Aneurysms*, NS20)

### Clinical Features of Spontaneous SAH
- sudden onset (seconds) of severe "thunderclap" H/A usually following exertion and described as the "worst headache of my life" (up to 97% sensitive, 12-25% specific)
- N/V, photophobia
- meningismus (neck pain/stiffness, positive Kernig's and Brudzinski's sign)
- decreased LOC (due to either raised ICP, ischemia, or seizure)

**Hunt and Hess Grade (clinical grading scale for SAH)**

| Grade | Description |
|---|---|
| 1 | No Sx or mild H/A and/or mild meningismus |
| 2 | Grade 1 + CN palsy |
| 3 | Confusion/lethargy, mild hemiparesis, or aphasia |
| 4 | GCS <15 but >8, moderate-severe hemiparesis, mild rigidity |
| 5 | Coma (GCS <9), decerebrate, moribund appearance |

Mortality of Grade 1-2 20%, increased with grade

- focal deficits: cranial nerve palsies (CN III, IV), hemiparesis
- ocular hemorrhage in 20-40% (due to sudden raised ICP compressing central retinal vein)
- reactive HTN
- sentinel bleeds
  - represents undiagnosed SAH
  - SAH-like symptoms lasting <1 d ("thunderclap H/A")
  - may have blood on CT or LP
  - ~30-60% of patients with full blown SAH give history suggestive of sentinel bleed within past 3 wk
- differential diagnosis: sentinel bleed, dissection/thrombosis of aneurysm, venous sinus thrombosis, benign cerebral vasculitis, benign exertional H/A

## Investigations

- non-contrast CT – for diagnosis of SAH
  - 98% sensitive within 12 h, 93% within 24 h; 100% specificity
  - may be negative if small bleed or presentation delayed several days
  - acute hydrocephalus, IVH, ICH, infarct or large aneurysm may be visible
- LP (highly sensitive) – for diagnosis of SAH if CT negative but high suspicion:
  - elevated opening pressure (>18 cm $H_2O$)
  - bloody initially, xanthochromic supernatant with centrifugation ("yellow") by ~12 h, lasts 2 wk
  - RBC count usually >100,000/mm3 without significant drop from first to last tube (in contrast to traumatic tap)
  - elevated protein due to blood breakdown products
- four vessel cerebral angiography ("gold standard" for aneurysms)
  - demonstrates source of SAH in 80-85% of cases
  - angiogram negative SAH: repeat angiogram in 7-14 d, if negative → "perimesencephalic SAH"
- MRA and CTA: sensitivity up to 95% for aneurysms, CTA>MRA for smaller aneurysms and delineating adjacent bony anatomy

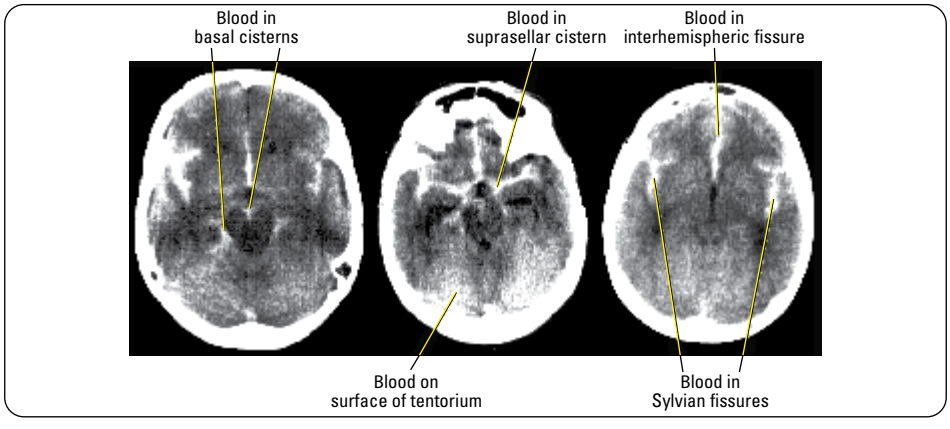



**Figure 19. Diagnosis of SAH**

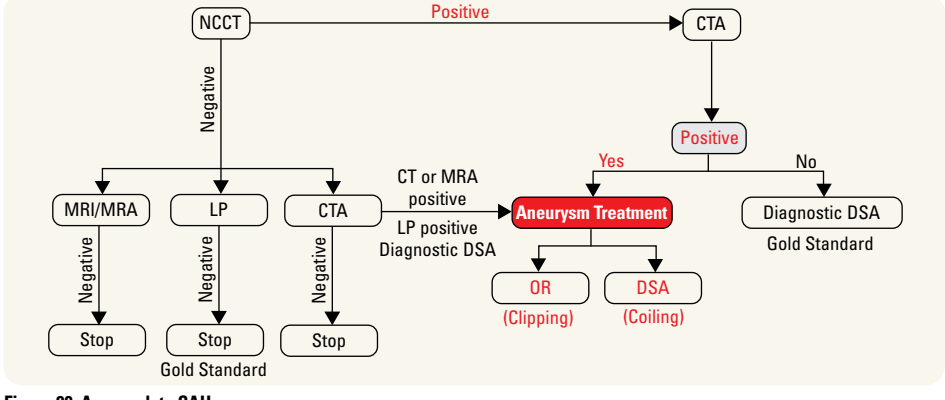



**Figure 20. Approach to SAH**
Adapted from: de Oliveira Manoel et al. (2014) Subarachnoid haemorrhage from a neuroimaging perspective. Critical Care

## Treatment

- admit to ICU or NICU
  - oxygen/ventilation prn
  - NPO, bed rest, elevate head of bed 30°, minimal external stimulation, neurological vitals q1h
  - aim to maintain sBP = 120-150 (balance of vasospasm prophylaxis, risk of rebleed, risk of hypotension since CBF autoregulation impaired by SAH)
  - cardiac rhythm monitor, Foley prn, strict monitoring of ins and outs

**World Federation of Neurological Surgeons Grading of SAH**

| WFNS Grade | GCS Score | Aphasia, Hemiparesis, or Hemiplegia |
|---|---|---|
| 0 * | | |
| 1 | 15 | – |
| 2 | 13-14 | – |
| 3 | 13-14 | + |
| 4 | 7-12 | + or – |
| 5 | 3-6 | + or – |

*Intact aneurysm

**Nontraumatic Subarachnoid Hemorrhage in the Setting of Negative Cranial Computed Tomography Results: External Validation of a Clinical and Imaging Prediction Rule**
Ann Emerg Med 2012;59:460-8.e1-7.doi:10.1016
**Background**: Two rules for SAH diagnosis exist. A clinical prediction rule states that patients with acute severe H/A but without the clinical variables age ≥40 yr, neck pain, LOC, or onset of H/A with exertion are at low risk for SAH. An imaging prediction rule bases diagnosis on non-contrast cranial CT for patients within 6 h of H/A onset.
**Methods**: Matched case-control study of 55 patients at 21 emergency departments between 2000 and 2011, and diagnoses were verified by LP.
**Results**: The clinical prediction rule for diagnosis of SAH was 97.1% sensitive, 22.7% specific, and had a negative likelihood ratio of 0.13. Using the imaging prediction rule resulted in a false negative rate of 20%.
**Conclusions**: Performing the clinical and imaging rules together has the potential for maximizing sensitivity of prediction and reducing rates of LP, but using imaging alone can result in missed cases.

**The Vasograde: A Simple Grading Scale For Prediction Of Delayed Cerebral Ischemia After Subarachnoid Hemorrhage**
Stroke 2015; 46(7):1826-31
**Background**: Patients are classically at risk of delayed cerebral ischemia (DCI) after aneurysmal SAH. We validated a grading scale – the VASOGRADE – for prediction of DCI.
**Method**: We used data of 3 phase II RCT and a single hospital series to assess the relationship between the VASOGRADE and DCI.
**Results**: In a cohort of 746 patients, the VASOGRADE signicantly predicted DCI (P<0.001). The VASOGRADE-Yellow had a tendency for increased risk for DCI (odds ratio [OR], 1.31; 95% CI, 0.77–2.23) when compared with VASOGRADE- Green; those with VASOGRADE-Red had a 3-fold higher risk of DCI (OR, 3.19; 95% CI, 2.07–4.50). VASOGRADE had an adequate discrimination for prediction of DCI (area under the receiver operating characteristics curve=0.63) and good calibration.
**Conclusions**: The VASOGRADE results validated previously published risk charts in a large and diverse sample of SAH patients, which allows DCI risk stratification on presentation after SAH. It could help to select patients at high risk of DCI, as well as standardize treatment protocols and research studies.

**The VASOGRADE**: A simple grading scale for prediction of delayed cerebral ischemia after SAH
*Stroke* 2015;46: 1826-1831

- medications
  - IV NS with 20 mmol KCl/L at 125-150 cc/h
  - nimodipine 60 mg PO/NG q4h x 21 d for delayed cerebral ischemia neuroprotection; may discontinue earlier if patient is clinically well
  - seizure prophylaxis: levetiracetam (Keppra®) 500 mg PO/IV q12h x 1 wk
  - mild sedation prn
  - neuroprotection
  - the only validated neuroprotective agent is nimodipine
  - studies on the use of IV magnesium and endothelin-A antagonist (clazosentan) showed reduction in DCI and vasospasm, respectively, without any effect on functional outcome
  - a trial on the use of statins did not show any neuroprotective benefit

**VASOGRADE**

| VASOGRADE | WFNS | Modified Fischer scale |
|---|---|---|
| **Green** | 1-2 | 1-2 |
| **Yellow** | 1-3 | 3-4 |
| **Red** | 4-5 | Any |

### Complications

- vasospasm: vasoconstriction and permanent pathological vascular changes in response to vessel irritation by blood – can lead to delayed cerebral ischemia and death
  - onset: 4-14 d post-SAH, peak at 6-8 d; most commonly due to SAH, rarely due to ICH/IVH
  - clinical features (new onset ischemic deficit): confusion, decreased LOC, focal deficit (speech or motor e.g. pronator drift)
  - risk factors: large amount of blood on CT (high Fisher grade), smoking, increased age, HTN
  - "symptomatic" vasospasm in 20-30% of SAH patients
  - "radiographic" vasospasm in 30-70% of arteriograms performed 7 d following SAH
  - diagnosed clinically, and/or with transcranial Doppler (increased velocity of blood flow)
  - risk of cerebral infarct and death
  - treatment
    - hyperdynamic ("triple H") therapy using fluids and pressors, usually after ruptured aneurysm has been clipped/coiled
    - direct vasodilation via angioplasty or intra-arterial verapamil for refractory cases
- delayed cerebral ischemia: neurological deterioration persisting more than 1 h in the absence of any obvious contributing physiological, radiological or laboratory abnormalities
  - peaks 4-10 d post ictus
  - can progress to cerebral infarction and is associated with significant morbidity and mortality
  - mechanism behind DCI is unclear but includes vasospasm, vascular dysautoregulation, neurotoxic effects from the blood, inflammation, micro-thrombi and cortical spreading depolarizations
  - it is an essential target for SAH management
- hydrocephalus (15-20%): due to blood obstructing arachnoid granules
  - can be acute or chronic, requires extraventricular drain or shunt, respectively
- neurogenic pulmonary edema
- hyponatremia: due to cerebral salt wasting (increased renal sodium loss and ECF volume loss), not SIADH
- DI
- cardiac: arrhythmia (>50% have ECG changes), MI, CHF

**Long-Term Risk of Recurrent Subarachnoid Hemorrhage, Death, Dependence and Standardized Mortality Ratios After Clipping or Coiling of an Intracranial Aneurysm (ISAT)**
Lancet 2015 Feb 21; 385(9969): 691–697
**Summary:**
1. The probability of death or dependency was significantly greater in the neurosurgical group (vs. endovascular group) at 10 year FU.
2. Rebleeding was more likely in endovascular group (vs. neurosurgical group), but risk was small at 10 year FU.
3. Probability of disability free survival was significantly greater in the endovascular group (vs. neurosurgical group) at 10 year FU.

**Methods**: RCT comparing endovascular coiling treatment with craniotomy and clipping for ruptured intracranial aneurysms in 2143 patients who were considered eligible for either modality or therapy between 1994-2002. 1644 patients were followed for deaths and outcomes for 10-18.5 years.
**Results**: At 10 years, 83% of endovascular coiling group and 79% of neurosurgical clipping group were alive. 82% of patients treated with endovascular coiling and 78% of patients treated with neurosurgical clipping were independent. Patients in the endovascular group were more likely to be alive and independent at 10 years vs. neurosurgery group (OR 1.34, 95% CI 1.07-1.67). Rebleeding risks from target aneurysm for endovascular group and neurosurgery group were 0.0216 (95% CI 0.0121-0.0383) and 0.0064 (95% CI 0.0024-0.0173), respectively.

### Prognosis

- 10-15% mortality before reaching hospital, overall 50% mortality (majority within first 2-3 wk)
- 30% of survivors have moderate to severe disability
- a major cause of mortality is rebleeding, for untreated aneurysms:
  - risk of rebleed: 4% on 1st day, 15-20% within 2 wk, 50% by 6 mo
  - if no rebleed by 6 mo, risk decreases to same incidence as unruptured aneurysm (2%)
  - only prevention is early clipping or coiling of "cold" aneurysm
  - rebleed risk for "perimesencephalic SAH" is approximately same as for general population

## Intracranial Aneurysms

### Epidemiology

- prevalence 1-4% (20% have multiple)
- F>M; age 35-65 yr (mean age of presentation is 50 years old)

**Commonest Locations of Saccular Aneurysms**
- AComm: 30%
- PComm: 25%
- MCA: 20%
- Basilar tip: 7%

### Types

- saccular (berry)
  - most common type
  - located at branch points of major cerebral arteries (Circle of Willis)
  - 85-95% in carotid (anterior) system, 5-15% in vertebrobasilar (posterior) circulation
- fusiform
  - atherosclerotic
  - more common in vertebrobasilar system, rarely rupture
- infectious
  - secondary to any infection of vessel wall, 20% multiple
  - 60% *Streptococcus* and *Staphylococcus*
  - 3-15% of patients with bacterial endocarditis

## Risk Factors

- autosomal dominant polycystic kidney disease (15%)
- fibromuscular dysplasia (7-21%)
- AVMs
- connective tissue diseases (Ehlers-Danlos, Marfan)
- family history
- bacterial endocarditis
- Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia)
- atherosclerosis and HTN
- trauma

**Risk Factors for Saccular (Berry) Aneurysms**
**S**moking
**H**ypetension
**A**dult Polycystic Kidney Disease
**E**hlers-Danlos Syndrome

**Table 12. Five Year Cumulative Rupture Risk in Unruptured Aneurysms Based on Size and Location**

| | Cavernous Carotid | AC/MC/IC | Vertebrobasilar/PC/PComm |
|---|---|---|---|
| **<7 mm** | 0% | 0% | 2.5% |
| **7-12 mm** | 0% | 2.6% | 14.5% |
| **13-24 mm** | 3% | 14.5% | 18.4% |
| **≥24 mm** | 6.4% | 40% | 50% |

AC = anterior cerebral/anterior communicating artery; IC = internal carotid artery; MC = middle cerebral artery; PC = posterior cerebral artery; PComm = posterior communicating artery.
Lancet 2003;362:103-110

**Long-Term, Serial Screening for Intracranial Aneurysms in Individuals with a Family History of Aneurysmal Subarachnoid Hemorrhage: A Cohort Study**
Lancet Neurol 2014;13:385-392
**Purpose**: To examine the yield of long-term serial screening for intracranial aneurysms for individuals with a positive family history of aneurysmal subarachnoid hemorrhage (aSAH) (two or more first degree relatives who have had aSAH or unruptured intracranial aneurysms).
**Study**: Screening results from April 1 1993 to April 1 2013 were reviewed in a cohort study. MRA or CTA was done from age 16-18 to 65-70 yr. After a negative screen, individuals were advised to contact the clinic in 5 yr for follow-up.
**Results**: Aneurysms were identified in 11% of individuals at first screening (n=458), 8% at second screening (n=261), 5% at third screening (n=128), and 5% at fourth screening (n=63). Smoking (OR 2.7, 95% CI 1.2-5.9), history of previous aneurysms (3.9, 1.2-12.7), and familial history of aneurysms (3.5, 1.6-8.1) were significant risk factors for aneurysm at first screening. History of previous aneurysms was the only significant risk factor for aneurysms at follow-up screening (HR 4.5, 95% CI 1.1-18.7).
**Conclusions**: The benefit of long-term screening in individuals with a family history of aSAH is substantial up to and after 10 yr of follow-up and two initial negative screens.

## Clinical Feature

- rupture (90%), most often SAH, but 30% ICH, 20% IVH, 3% subdural bleed
- sentinel hemorrhage ("thunderclap H/A") → requires urgent clipping/coiling to prevent catastrophic bleed
- mass effect (giant aneurysms)
  - internal carotid or anterior communicating aneurysm may compress:
    - the pituitary stalk or hypothalamus causing hypopituitarism
    - the optic nerve or chiasm producing a visual field defect
    - basilar artery aneurysm may compress midbrain, pons (limb weakness), or CN III
    - posterior communicating artery aneurysm may produce CN III palsy
    - intracavernous aneurysms (CN III, IV, V1, V2, VI)
- distal embolization (e.g. amaurosis fugax)
- seizures
- H/A (without hemorrhage)
- incidental CT or angiography finding (asymptomatic)

## Investigations

- CT angiogram (CTA), magnetic resonance angiography (MRA), cerebral angiogram

## Treatment

- **ruptured aneurysms**
  - overall trend towards better outcome with early surgery or coiling (48-96 h after SAH)
    - treatment options: surgical placement of clip across aneurysm neck, trapping (clipping of proximal and distal vessels), thrombosing using Guglielmi detachable coils (coiling) or flow diversion stents, wrapping (last resort)
  - choice of surgery vs. coiling not yet well defined: consider location, size, shape, and tortuosity of the aneurysm, patient comorbidities, age, and neurological condition; in general:
    - coiling: posterior > anterior circulation, deep/eloquent location, basilar artery bifurcation/apex, older age, presence of comorbidities, presence of vasospasm
    - clipping: superficial > deep, broad aneurysmal base, branching arteries at the aneurysm base, tortuosity/atherosclerosis of afferent vessels, dissection, hematoma, acute brainstem compression
- **unruptured aneurysms**
  - average 1% annual risk of rupture: risk dependent on size and location of aneurysm
  - no clear evidence on when to operate: need to weigh life expectancy
  - risk of morbidity/mortality of SAH (20%-50%) vs. surgical risk (2%-5%)
  - generally treat unruptured aneurysms >10 mm
  - consider treating when aneurysm 7-9 mm in middle-aged, younger patients, or patients with a family history of aneurysms
  - follow smaller aneurysms with serial angiography

**The Unruptured Intracranial Aneurysm Treatment Score**
Neurology 2015;85(10):881-9
**Objective**: to develop an unruptured intracranial aneurysm (UIA) treatment score (UIATS) model that includes and quantifies key factors involved in clinical decision-making in the management of UIAs and to assess agreement for this model among specialists in UIA management and research.
**Methods**: An international multidisciplinary (neurosurgery, neuroradiology, neurology, clinical epidemiology) group of 69 specialists was convened to develop and validate the UIATS model using a Delphi consensus method.
**Results**: The UIATS accounts for 29 key factors in UIA management.
**Conclusions**: This novel UIA decision guidance study captures an excellent consensus among highly informed individuals on UIA management, irrespective of their underlying specialty.

# Intracerebral Hemorrhage

## Definition
- hemorrhage within brain parenchyma, accounts for ~10% of strokes
- can dissect into ventricular system (IVH) or through cortical surface (SAH)

## Etiology
- HTN (usually causes bleeds at putamen, thalamus, pons, and cerebellum)
- hemorrhagic transformation (reperfusion post stroke, surgery, strenuous exercise, etc.)
- vascular anomalies
  - aneurysm, AVMs, and other vascular malformations (see *Vascular Malformations*, NS23)
  - venous sinus thrombosis
  - arteriopathies (cerebral amyloid angiopathy, lipohyalinosis, vasculitis)
- tumours (1%): often malignant (e.g. glioblastoma multiforme, lymphoma, metastases)
- drugs (amphetamines, cocaine, alcohol, anticoagulants, etc.)
- coagulopathy (iatrogenic, leukemia, thrombotic thrombocytopenic purpura, aplastic anemia)
- CNS infections (fungal, granulomas, herpes simplex encephalitis)
- post trauma (immediate or delayed, frontal and temporal lobes most commonly injured via coup-contrecoup mechanism)
- eclampsia
- post-operative (post-carotid endarterectomy cerebral reperfusion, craniotomy)
- idiopathic

## Epidemiology
- 12-31 cases/100,000 population/yr

## Risk Factors
- increasing age (mainly >55 yr)
- male gender
- HTN
- Black/Asian > Caucasian
- previous CVA of any type (23x risk)
- both acute and chronic heavy alcohol use; cocaine, amphetamines
- liver disease
- anticoagulants

## Clinical Features
- TIA-like symptoms often precede ICH, can localize to site of impending hemorrhage
- gradual onset of symptoms over minutes-hours, usually during activity
- H/A, N/V, and decreased LOC are common
- specific symptoms/deficits depend on location of ICH

## Investigations
- baseline severity score such as the ICH Score should be performed as part of the initial workup
- hyperdense blood on non-contrast CT
- CTA routine, if spot sign (contrast in the hematoma) demonstrated there is high likelihood of clot growth

## Treatment
- patients should be transferred to and managed in a neuro-ICU or stroke unit
- **medical**
  - decrease MAP to pre-morbid level or by ~20% (target BP 140/90) in ED
  - check PTT/INR, and correct coagulopathy (immediate reversal of anticoagulation)
  - control raised ICP (see *Intracranial Pressure Dynamics*, NS4)
  - corticosteroids should NOT be used for elevated ICP in ICH
  - levetiracetam/phenytoin for seizure prophylaxis
  - follow electrolytes (SIADH common)
  - angiogram to rule out vascular lesion unless >45 yr, known HTN, and putamen/thalamic/posterior fossa ICH (yield ~0%)
- **surgical**
  - craniotomy with evacuation of clot, treatment of source of ICH (i.e. AVM, tumour, cavernoma), ventriculostomy to treat hydrocephalus
  - indications
    - symptoms of raised ICP or mass effect
    - rapid deterioration (especially if signs of brainstem compression)
    - favourable location (e.g. cerebellar, non-dominant hemisphere)
    - young patient (<50 yr)
    - if tumour, AVM, aneurysm, or cavernoma suspected (resection or clip to decrease risk of rebleed)
  - contraindications
    - small bleed: minimal symptoms, GCS >10
    - poor prognosis: massive hemorrhage (especially dominant lobe), low GCS/coma, lost brainstem function
    - medical reasons (e.g. very elderly, severe coagulopathy, difficult location [e.g. basal ganglia, thalamus])

**Location of ICH**
Basal Ganglia/Internal Capsule (50%)
Thalamus (15%)
Cerebral White Matter (15%)
Cerebellum/Brainstem – usually pons (15%)
Other (5%)

**ICH Score Components**
- GCS score (3-4 = 2 pts; 5-12=1 pt, 13-15=0 pt)
- ICH volume (≥30 cm= 1 pt, <30 cm= 0 pt)
- Presence of IVH (yes=1 pt, no=0 pt)
- Infratentorial origin (yes=1 pt, no=0 pt)
- Age (≥80 = 1 pt, <80 = 0 pt)

**Early Surgery vs. Initial Conservative Treatment in Patients with Spontaneous Supratentorial Lobar Intracerebral Hematomas (STICH-II): A Randomized Trial**
Lancet 2013 382(9890): 397-408
**Summary**: The STICH II (international, parallel-group trial comparing early surgical hematoma evacuation within 12 hour of randomization and medical treatment vs. initial medical treatment alone) results confirm that early surgery does not increase the rate of death or disability at 6 mo and might have a small but clinically relevant survival advantage for patients with spontaneous superficial intracerebral haemorrhage without intraventricular haemorrhage.

**Spetzler-Martin AVM Grading Scale**

| Item | Score |
|---|---|
| **Size** | |
| 0-3 cm | 1 |
| 3.1-6.0 cm | 2 |
| >6 cm | 3 |
| **Location** | |
| Noneloquent | 0 |
| Eloquent | 1 |
| **Deep Venous Drainage** | |
| Not present | 0 |
| Present | 1 |

AVM grades calculated by adding the 3 individual Spetzler-Martin Scale scores from the above table. e.g. a 2 cm tumour in noneloquent location without deep venous drainage = Grade I

### Prognosis
- 30 d mortality rate 44%, mostly due to cerebral herniation
- rebleed rate 2-6%, higher if HTN poorly controlled

# Vascular Malformations

### Types
- AVMs
- cavernous malformations (cavernomas, cavernous hemangiomas/angiomas)
- venous angioma
- capillary telangiectasias
- AVF (carotid-cavernous fistula, dural AVF, vein of Galen aneurysm)
- "angiographically occult vascular malformations" (any type, 10% of malformations)

## Arteriovenous Malformations, Cavernous Malformations, and Dural Fistulas

**Table 13. Comparison of Pathoetiology, Clinical Feature, and Treatment of Arteriovenous Malformations, Cavernous Malformations, and Dural Fistulas**

| | Arteriovenous Malformation | Cavernous Malformations | Dural Fistulas |
|---|---|---|---|
| **Definition** | Tangle of abnormal vessels/arteriovenous shunts, with no intervening capillary beds or brain parenchyma; usually congenital | Benign vascular hamartoma consisting of irregular sinusoidal vascular channels located within the brain without intervening neural tissue or associated large arteries/veins<br>Several genes now described: CCM1, CCM2, CCM3 | Fistula's connecting dural arteries to dural veins or the dural sinus<br>Frequently described to occur at the transverse and cavernous sinuses, but can be found at every cranial dural sinus<br>Hypothesized to be related to venous sinus thrombosis formation, and subsequent microvascular shunt formation within the dura between arteries and veins |
| **Epidemiology** | Prevalence ~0.14%, M:F = 2:1, average age at diagnosis = 33 yr<br>15-20% of patients with hereditary hemorrhagic telengiectasia (Osler-Weber-Rendu syndrome) will have cerebral AVMs | Prevalence of 0.1-0.2%, both sporadic and hereditary forms described | Unknown true incidence<br>Constitute 10-15% of all intracranial vascular abnormalities |
| **Clinical Features** | Hemorrhage (40-60%): small AVMs are more likely to bleed due to direct high pressure AV connections<br>Seizures (50%): more common with larger AVMs<br>Mass effect<br>Focal neurological signs secondary to ischemia (high flow → "steal phenomena")<br>Localized headache, increased ICP<br>Bruit (especially with dural AVMs)<br>May be asymptomatic ("silent") | Seizures (60%), progressive neurological deficit (50%), hemorrhage (20%), H/A<br>Often an incidental finding<br>Hemorrhage risk less than AVM, usually minor bleeds | Asymptomatic, pulsatile tinnitus if involving sigmoid or transverse sinuses, bruits, H/A<br>Carotid cavernous involvement classically produces proptosis, chemosis, and bruits<br>Symptoms of SAH, SDH, or ICH |
| **Investigations** | MRI (flow void), MRA<br>Angiography (7% will also have one or more associated aneurysms) | T2WI MRI (non-enhancing)<br>Gradient echo sequencing (best for diagnosis) | Non-enhanced CT to r/o hemorrhage<br>MRI; however, this does not demonstrate the arterial supply to the fistula<br>Angiography remains the gold standard |
| **Treatment** | Decreases risk of future hemorrhage and seizure<br>Surgical excision is treatment of choice even in Spetzler-Martin Grades I – II with general good health<br>SRS is preferred for small (<3 cm) or very deep lesions<br>Endovascular embolization (glue, balloon) can be curative (5%) or used as adjuvant to surgery or SRS in larger lesions<br>Conservative (e.g. palliative embolization, seizure control if necessary) | Surgical excision:<br>Only appropriate for symptomatic lesions that are surgically accessible (supratentorial lesions are less likely to bleed than infratentorial lesions) | Approach is dependent on size, location and symptoms, and includes:<br>Conservative treatment<br>Neuroradiological endovascular interventions<br>Radiation therapy<br>Surgery<br>Combination of the above |
| **Prognosis** | 10% mortality, 30-50% morbidity (serious neurological deficit) per bleed<br>Risk of major bleed in untreated AVMs: 2-4%/yr | Annual bleeding rates: 0.25-1.1% for supratentorial, 2-3% for brainstem<br>Symptomatic lesions have a higher hemorrhage risk than asymptomatic | 8.1% annual risk of hemorrhage<br>6.9% annual risk for non-hemorrhagic neurological deficit<br>10.4% mortality rate |

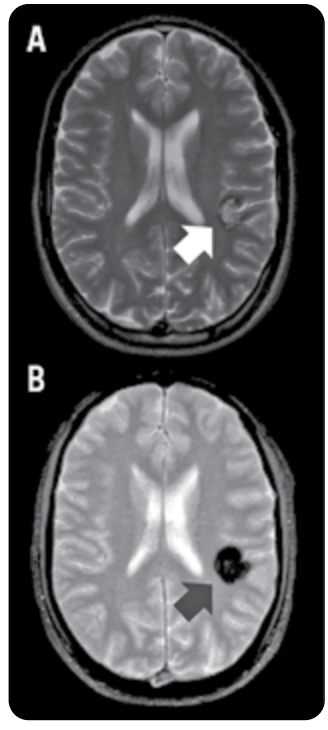



**Figure 21. MRI of cavernous malformation**
A. T2 weighted imaging MRI
B. Gradient echo sequencing MRI

**Clinical Course of Untreated Cerebral Cavernous Malformations (CCM)**
Lancet Neurol 2015 pii: S1474-4422(15)00303-8
**Summary**: (1) mode of clinical presentation and (2) CCM location are independently associated with ICH within 5 yr of CCM diagnosis. The risk of recurrent hemorrhage from a CCM is greater than the risk of first event and declines over 5 yr.
**Methods**: Collected individual patient data from investigators of published studies on MEDLINE and Embase since inception until April 2015 (7 cohorts from 6 studies, n=1620) on clinical course from CCM diagnosis until first CCM treatment or last available follow-up.
**Results**: 204 of 1620 experienced ICH during 5187 person-year follow-up (Kaplan-Meier estimated 5-year risk 15.8%, 95% CI 13.7-17.9). ICH within 5 yr of CCM was associated with clinical presentation with ICH or focal neurological deficit without brain imaging evidence of recent hemorrhage (vs. other presentations; HR 5.6, 95% CI 3.2-9.7) and with brainstem CCM location (vs. other locations; HR 4.4, 95% CI 2.3-8.6).

# Cerebrospinal Fluid Fistulas

### Etiology
- cranial or spinal
- traumatic: after head trauma, iatrogenic (post-transsphenoidal surgery, post skull base surgery)
- nontraumatic: high pressure (hydrocephalus, tumour), normal pressure (bone erosion secondary to infection, congenital defect)

### Clinical Features
- otorrhea or rhinorrhea (clear fluid)
- low pressure H/A (worse when sitting up)
- confirmatory testing for CSF: β transferrin test, quantitative glucose analysis of fluid, "ring sign", "reservoir sign"

### Investigations
- CT (detect pneumocephalus, fractures, skull base defects), water contrast CT cisternography

### Treatment
- lower ICP (avoid straining, acetazolamide to reduce CSF production, modest fluid restriction)
- persistent leak: may require continuous lumbar drainage via percutaneous catheter
- surgical indications: traumatic leak lasting >2 wk, spontaneous leaks, delayed onset of leak after trauma or surgery, leaks complicated by meningitis

Suspect CSF fistula in patients with otorrhea or rhinorrhea after head trauma or recurrent meningitis

**Ring Sign**: If CSF is stringed with blood. Allow CSF to drain onto the surrounding sheets; positive if clear in centre with surrounding blood coloured ring (double ring sign)
**Reservoir Sign**: Gush of CSF leaks out in certain head positions; i.e. teapot sign (not specific or sensitive)

**Stereotactic Radiosurgery for Cavernous Malformations (CM)**
J Neurosurg. 2010;113(4):691-9
**Summary**: SRS is a safe intervention for CMs, with advantages of reducing rebleed risks in patients with repeated pretreatment hemorrhage. Treating CMs with single bleed is less clear. However, the morbidity of repeated hemorrhage outweights any radiosurgery related morbidity and early active management of deep-seated CMs should be considered.
**Methods**: Retrospective analysis of 113 patients with 79 brainstem and 39 thalamic/basal ganglia CMs treated with gamma knife surgery.
**Results:**
1. Patients with multiple symptomatic hemorrhages before radiosurgery (n=41): rebleed rate decreased from 30.5% per lesion to 15% for the first 2 years after radiosurgery and 2.4% subsequently. Pretreatment multiple bleeds led to permanent deficits in 72% of these patients.
2. Patients with ≤1 symptomatic bleed before radiosurgery (n=77): natural history is uncertain due to short period between presenting bleed and treatment (median 1 year). Rate of hemorrhage was 5.1% for the first 2 years and 1.3% subsequently. Pretreatment hemorrhages led to permanent deficits in 43% of these patients (significantly lower than multiple-bleeds group, p<0.001).
3. Permanent adverse radiation effects were rare (7.3%) and minor in both groups.
4. Posttreatment hemorrhages led to persistent deficits in 7.3% of patients.

**RED FLAGS for Back Pain**
**BACK PAIN**
**B**owel/**B**ladder (retention or incontinence)
**A**nesthesia (saddle)
**C**onstitutional symptoms
"**K**"hronic disease
**P**arasthesia
**A**ge >50 yr or <20 yr
**I**V drug use
**N**euromotor deficits
**Cauda Equina**
- Urinary retention or incontinence, fecal incontinence or loss of anal sphincter tone, saddle anesthesia, uni/bilateral, leg weakness/pain

**Malignancy**
- Age >50 yr, previous Hx of cancer, pain unrelieved by bed rest, constitutional symptoms

**Infection**
- Increased ESR, IV drug use, immunosuppressed, fever

**Compression Fracture**
- Age >50 yr, trauma, prolonged steroid use

# EXTRACRANIAL PATHOLOGY

# Approach to Limb/Back Pain

- see Orthopedic Surgery, OR3

# Extradural Lesions

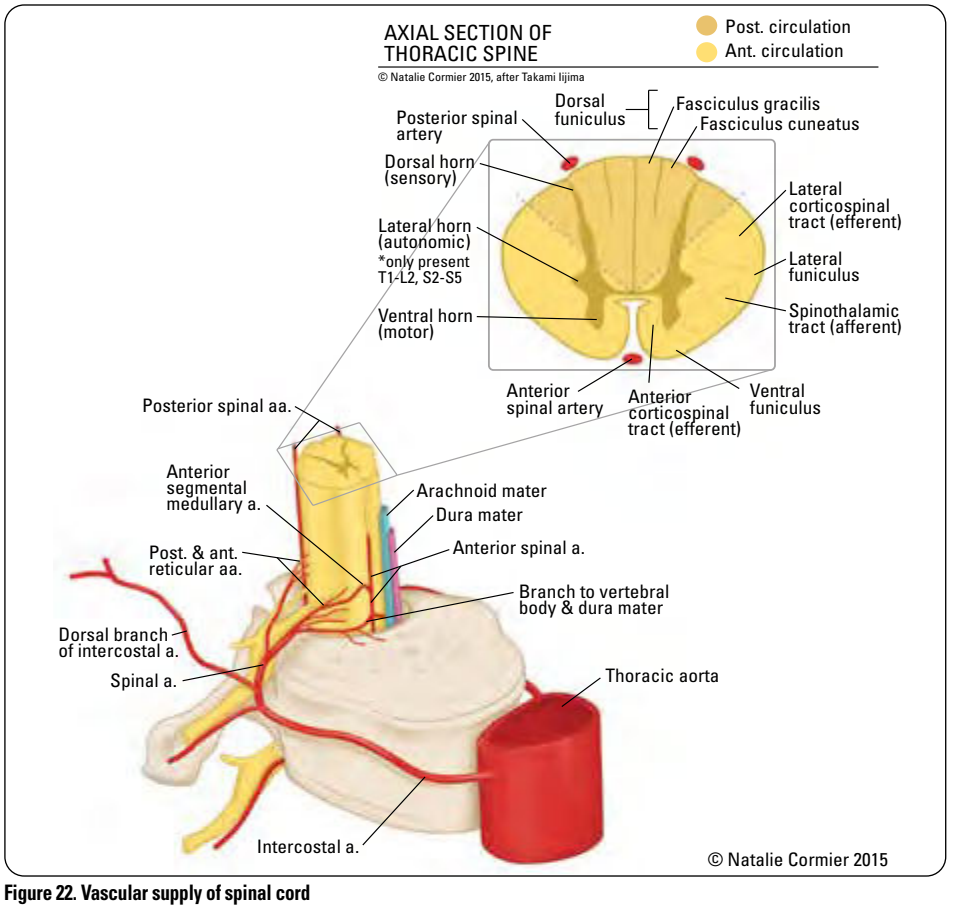



**Figure 22. Vascular supply of spinal cord**

# Root Compression

- radiculopathy is a pain and/or sensorimotor deficit syndrome that involves compression of a nerve root. Nerve compression generally occurs as a result of disc herniation, degenerative disc diseases (spondylosis), instability, and rarely, masses
- patients generally present with referred pain, sensory changes (numbness and/or tingling) or weakness. Whereas patients might sometime describe sensory changes in a dermatomal distribution, the referred pain will not be in a dermatomal distribution. The areas of pain and altered sensorium may be incongruent
- muscle innervation has less overlap than sensory innervation and hence is a better predictor of level of pathology



**Sensory Fibres**
Fasciculus gracilis/cuneatus: proprioception, fine touch, vibration
Spinothalamic tract: pain and temperature
**Motor Fibres**
Corticospinal tract: skilled movements

### Differential Diagnosis
- herniated disc
- neoplasm (neurofibroma, schwannoma)
- synovial cyst, abscess
- hypertrophic bone/spur

# Cervical Disc Syndrome

### Etiology
- nucleus pulposus herniates through annulus fibrosus and impinges upon nerve root, most commonly at C6-C7 (C7 root)



Disc herniations impinge the nerve root at the level **below** the interspace (i.e. C5-6 disc affects the C6 nerve root)

### Clinical Features
- pain in arm follows nerve root distribution, worse with neck extension, ipsilateral rotation, and lateral flexion (all compress the ipsilateral neural foramen)
- LMN signs and symptoms
- central cervical disc protrusion causes myelopathy as well as nerve root deficits

### Investigations
- if red flags: C-spine x-ray, CT, MRI (imaging of choice)
- only consider EMG/nerve conduction studies if diagnosis uncertain and presenting more as peripheral nerve issue

### Treatment
- conservative
  - no bedrest unless severe radicular symptoms
  - activity modification, patient education (reduce sitting, lifting)
  - physiotherapy, exercise programs focus on strengthening core muscles
  - analgesics; NSAIDs are more efficacious
  - avoid cervical manipulation like traction
- surgical indications
  - anterior cervical discectomy is the usual approach (posterior formanotomy with discectomy is the other option)
  - intractable pain despite adequate conservative treatment for >3 mo
  - progressive neurological deficit

### Prognosis
- 95% improve spontaneously in 4-8 wk

**Table 14. Lateral Cervical Disc Syndromes**

| | C4-5 | C5-6 | C6-7 | C7-T1 |
|---|---|---|---|---|
| **Root Involved** | C5 | C6 | C7 | C8 |
| **Incidence** | 2% | 19% | 69% | 10% |
| **Sensory** | Shoulder | Thumb | Middle finger | Ring finger, 5th finger |
| **Motor** | Deltoid, biceps, supraspinatus | Biceps, wrist extensors | Triceps | Digital flexors, intrinsics |
| **Reflex** | No change | Biceps, brachioradialis | Triceps | Finger jerk (Hoffmann's sign) |

# Cervical Spondylosis

### Definition
- progressive degenerative process of cervical spine leading to canal stenosis – congenital spinal stenosis, degeneration of intervertebral discs, hypertrophy of lamina, dura, or ligaments, subluxation, altered mobility, telescoping of the spine due to loss of height of vertebral bodies, alteration of normal lordotic curvature
- resultant syndromes: mechanical neck pain, radiculopathy (root compression), myelopathy (spinal cord compression)

Cervical spondylotic myelopathy is the most common cause of spinal cord impairment

### Epidemiology
- typically begins at age 40-50, M>F, most commonly at the C5-C6 > C6-C7 levels

### Pathogenesis
- any of: disc degeneration/herniation, osteophyte formation, ossification, and hypertrophy of ligaments
- pathophysiology includes static compression, dynamic compression, and vascular compromise

### Clinical Features
- insidious onset of mechanical neck pain exacerbated by excess vertebral motion (particularly rotation and lateral bending with a vertical compressive force – Spurling's test)
- the earliest symptoms are gait disturbance and lower extremity weakness or stiffness
- occipital H/A is common
- radiculopathy may involve 1 or more roots, and symptoms include neck, shoulder, and arm pain, paresthesias, and numbness
- cervical spondylotic myelopathy may present with:
  - weakness (upper > lower extremity), lower extremity weakness (corticospinal tracts) is most worrisome complaint
  - decreased dexterity, loss of fine motor control
  - sensory changes
  - UMN findings such as hyperreflexia, clonus, and Babinski reflex
  - funicular pain, characterized by burning and stinging ± Lhermitte's sign (lightning-like sensation down the back with neck flexion)

**Clinical Grading Scores to Assess CSM**
- mJOA
- Nurick Grade
- Neck Disability Index

### Investigations
- x-ray of cervical spine ± flexion/extension (alignment, fractures)
- MRI most useful for determination of compression of the neural element
- CT is only used for better determination of bony anatomy (i.e. OPLL)
- EMG/nerve conduction studies reserved for peripheral nerve investigation

**A Clinical Practice Guideline for the Management of Patients with Degenerative Cervical Myelopathy (Dcm): Recommendations for Patients with Mild, Moderate, and Severe Disease and Nonmyelopathic Patients with Evidence of Cord Compression**
Global Spine Journal 2017; 7(3S):70S-83S
**Severe and moderate DCM**: Moderate evidence suggesting strong recommendation of surgical intervention.
**Mild DCM**: Very low to low evidence suggesting offering surgical intervention or a structured rehabilitation and if non-operative management initially pursued, consider operative intervention if evidence of neurological deterioration.
**Non-myelopathic patients without radiculopathy**: In such patients with imaging evidence of cervical cord compression, suggestion of not offering prophylactic surgery; counsel, educate, and follow clinically.
**Non-myelopathic patients with radiculopathy**: Such patients with imaging evidence of cervical cord compression are at a higher risk of developing myelopathy and should be counselled. Offer surgical or nonoperative treatment with appropriate follow-up and structured rehabilitation.

### Treatment
- nonsurgical: physiotherapy, anti-inflammatory medications
- surgical: anterior approach (anterior cervical discectomy or corpectomy), posterior approach (decompressive cervical laminectomy)
- in multilevel CSM, an anterior approach is associated with better postoperative neural function but has a higher complication and reoperation rate than the posterior group
- surgical indications: myelopathy with motor impairment, progressive neurologic impairment, intractable pain
- complete remission almost never occurs; surgical decompression may stop progression of disease

# Lumbar Disc Syndrome

### Definition
- compression of nerve roots caused by herniation of the nucleus pulposus through the annulus fibrosus of an intervertebral disc in the lumbar spine

### Etiology
- posteriolaterally herniated disc compressed nerve root exiting BELOW the level of the disc or the traversing nerve root
- far lateral disc herniation compressed nerve root AT the level of the disc or the exiting nerve root
- central herniation causes cauda equina or lumbar stenosis (neurogenic claudication)

### Clinical Features
- initially back pain, then leg pain > back pain
- limited back movement (especially forward flexion) due to pain
- motor weakness, dermatomal sensory changes, decreased reflexes
- exacerbation with valsalva; relief with flexing the knee or thigh
- nerve root tension signs
  - straight leg raise (Lasegue's test) or crossed SLR (pain should occur at less than 60°) suggests L5, S1 root involvement
  - femoral stretch test suggests L2, L3, or L4 root involvement

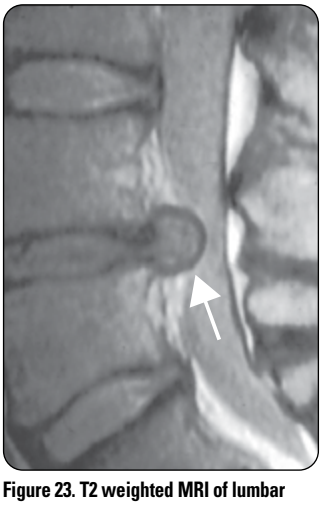


**Figure 23. T2 weighted MRI of lumbar disc herniation**

### Investigations
- MRI is modality of choice
- x-ray spine (only to rule out other lesions), CT (bony anatomy)
- myelogram and post-myelogram CT (only if MRI is contraindicated)

### Treatment
- conservative (same as cervical disc disease)
- surgical indications: same as cervical disc and cauda equina syndrome

### Prognosis
- 95% improve spontaneously within 4-8 wk
- those who do not improve with conservative treatment achieve symptom relief quicker with surgery than continuation of conservative management; however, the long-term outcome after surgery is comparable to conservative therapy
- do not follow patients with serial MRIs; clinical status is more important at guiding management

**Table 15. Lateral Lumbar Disc Syndromes**

| | L3-4 | L4-5 | L5-S1 |
|---|---|---|---|
| **Root Involved** | L4 | L5 | S1 |
| **Incidence** | <10% | 45% | 45% |
| **Pain** | Femoral pattern | Sciatic pattern | Sciatic pattern |
| **Sensory** | Medial leg | Dorsal foot to hallux<br>Lateral leg | Lateral foot |
| **Motor** | Tibialis anterior (dorsiflexion) | Extensor hallucis longus (hallux extension) | Gastrocnemius, soleus (plantar flexion) |
| **Reflex** | Patellar | Medial hamstrings | Achilles |

**Table 16. Differentiating Conus Medullaris Syndrome from Cauda Equina Syndrome**

| | Conus Medullaris Syndrome | Cauda Equina Syndrome |
|---|---|---|
| **Onset** | Sudden, bilateral | Gradual, unilateral |
| **Spontaneous Pain** | Rare, if present usually bilateral, symmetric in perineum or thighs | Severe, radicular type: in perineum, thighs, legs, back, or bladder |
| **Sensory Deficit** | Saddle; bilateral and symmetric; sensory dissociation | Saddle; no sensory dissociation; may be unilateral and asymmetric |
| **Motor Deficit** | Symmetric; paresis less marked; fasciculations may be present | Asymmetric; paresis more marked; atrophy may be present; fasciculations rare |
| **Reflexes** | Only ankle jerk absent (preserved knee jerk) | Knee and ankle jerk may be absent |
| **Autonomic Symptoms (bladder dysfunction, impotence, etc.)** | Urinary retention and atonic anal sphincter prominent early; impotence frequent | Sphincter dysfunction presents late; impotence less frequent |

# Cauda Equina Syndrome

### Etiology
- compression or irritation of lumbosacral nerve roots below conus medullaris (below L2 level)
- decreased space in the vertebral canal below L2
- common causes: herniated disc ± spinal stenosis, vertebral fracture, and tumour

### Clinical Features
- usually acute (develops in less than 24 h); rarely subacute or chronic
- motor (LMN signs)
  - weakness in multiple root distribution
  - reduced deep tendon reflexes (knee or ankle)
- autonomic
  - urinary retention (or overflow incontinence) and/or fecal incontinence due to loss of anal sphincter tone
- sensory
  - low back pain radiating to legs (sciatica) aggravated by Valsalva maneuver and by sitting; relieved by lying down
  - bilateral sensory loss or pain: depends on the level affected
  - saddle area (S2-S5) anesthesia
  - sexual dysfunction (late finding)

### Investigations
- urgent MRI to confirm compression of S2-S3-S4 nerve root by a large disc herniation
- post-void residual very helpful to determine if true retention is present; volumes controversial but anything over 250 cc in a healthy individual is cause for concerns



**Surgical versus Non-Operative Treatment for Lumbar Disc Herniation: Eight-Year Results for the Spine Patient Outcomes Research Trial (SPORT)**
Spine 2014; 39(1): 3-16
**Methods**: In the RCT arm of the study, 501 patients with imaging-confirmed lumbar disc herniation were randomized to open discectomy versus standard non-operative management.
**Results**: Surgery was superior in intent-to-treat analysis for sciatica severity (p=0.005), patient satisfaction (p=0.013), and self-rated improvement (p=0.013) at 8 year follow-up. Improvements in pain, physical function, and disability were only seen in an as-treated analysis due to significant non-adherence to treatment assignment.
**Conclusion**: Patients who are carefully selected for surgical intervention show greater symptom improvement compared to non-operative management.



**Magnetic Resonance Imaging in Follow-Up Assessment of Sciatica**
NEJM 2013;368:999-1007
**Background**: Follow-up MRI is a controversial method for monitoring sciatica in patients with known lumbar-disc herniation.
**Methods**: Participants (n=283) were recruited from a simultaneous, parallel, randomized study comparing surgery and conservative care for sciatica (the Sciatica Trial). MRI and clinical assessment were undertaken pre-treatment and 1 yr post-treatment randomization to visualize disc herniation and evaluate outcome.
**Results**: At 1 yr, disc herniation was visible in 35% with a favourable outcome (complete, or nearly complete symptom resolution) and in 33% with an unfavourable outcome (p=0.70). A favourable outcome was reported in 85% of patients with disc herniation and 83% without disc herniation (p=0.70).
**Conclusions**: Anatomical abnormalities visible on repeated MRI 1 yr after treatment for sciatica due to lumbar-disc herniation could not distinguish patients with resolution of their symptoms from patients still experiencing symptoms.



**Causes of Cauda Equina Syndrome**
- Lumbar disc herniation
- Spinal stenosis
- Spinal tumour
- Epidural abscess
- Hematoma
- Trauma

### Treatment
- surgical decompression (<48 h) to preserve bowel, bladder, and sexual function, and/or to prevent progression to paraplegia
- consult radiation oncology for urgent symptomatic management if palliative oncology patient

### Prognosis
- markedly improves with surgical decompression
- recovery correlates with function at initial presentation: if patient is ambulatory, likely to continue to be ambulatory; if unable to walk, unlikely to walk after surgery

## Lumbar Spinal Stenosis

### Etiology
- congenital narrowing of spinal canal combined with degenerative changes (herniated disc, hypertrophied facet joints, and ligamentum flavum)

### Clinical Features
- gradually progressive back and leg pain with standing and walking that is relieved by sitting or lying down (neurogenic claudication – 60% sensitive)
- neurologic exam may be normal, including straight leg raise test

### Investigations
- MRI is the optimal investigation to confirm and localize the level of stenosis (unlike nerve root compression which can be localized with clinical exam)

### Treatment
- conservative: NSAIDs, analgesia, physical therapy
- surgical: laminectomy with root decompression (the role of fusion may need to be considered if the amount of bone removed with the laminectomy results in destabilization)

**Long-Term Outcomes of Lumbar Spinal Stenosis: Eight-Year Results of the Spine Patient Outcomes Research Trial (SPORT)**
Spine 2015; 40(2): 63–76
**Methods**: In the RCT arm of the study, 289 patients were randomized to decompressive laminectomy (n=138) or standard non-operative care (n=151).
**Results**: Intent-to-treat analyses showed no difference in pain, physical function, and disability outcome measures, because 52% randomized to non-operative management had undergone surgery at 8 years. As-treated analyses showed early benefits for surgery until 4 years, however effects in primary outcomes converged between years 5-8.
**Conclusion**: Decompressive laminectomy for symptomatic spinal stenosis may show diminishing symptomatic benefits beyond 4 years.

## Neurogenic Claudication

### Etiology
- ischemia of lumbosacral nerve roots secondary to vascular compromise and increased demand from exertion, often associated with lumbar stenosis

### Clinical Features
- dermatomal pain/paresthesia/weakness of buttock, hip, thigh, or leg initiated by standing or walking
- slow relief with postural changes (sitting >30 min), NOT simply exertion cessation
- induced by variable degrees of exercise or standing
- may be elicited with lumbar extension, but may not have any other neurological findings, no signs of vascular compromise (e.g. ulcers, poor capillary refill, etc.)

### Investigations
- bicycle test may help distinguish neurogenic claudication (NC) from vascular claudication (the waist-flexed individuals on the bicycle with NC can last longer)

### Treatment
- same as for lumbar spinal stenosis

**Key Features of Neurogenic vs. Vascular Claudication**
**Neurogenic Claudication**: dermatomal distribution with positional relief occurring over minutes
**Vascular Claudication**: sclerotomal distribution with relief occurring with rest over seconds

# Intradural Intramedullary Lesions

## Syringomyelia (Syrinx)

### Definition
- cystic cavitation of the spinal cord
- presentation is highly variable, usually progresses over months to years
- initially pain, weakness; later atrophy and loss of pain and temperature sensation

### Etiology
- 70% are associated with Chiari I malformation, 10% with basilar invagination
- post-traumatic
- tumour
- tethered cord

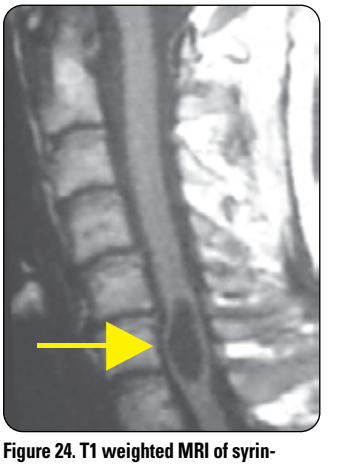


**Figure 24. T1 weighted MRI of syringomyelia**

### Clinical Features
- nonspecific features for any intramedullary spinal cord pathology:
  - initially pain, weakness, atrophy, then loss of pain and temperature (spinothalamic tract) in upper extremities (central syrinx) with progressive myelopathy over years
  - sensory loss with preserved touch and proprioception (dorsal column–medial lemniscus pathway) in a band-like distribution at the level of cervical syrinx
  - dysesthetic pain often occurs in the distribution of the sensory loss
  - LMN arm/hand weakness or wasting
  - painless neuropathic arthropathies (Charcot's joints), especially in the shoulder and neck due to loss of pain and temperature sensation

### Investigations
- MRI is best method, myelogram with delayed CT

### Treatment
- treat underlying cause (e.g. posterior fossa decompression for Chiari I, surgical removal of tumour if causing a syrinx)
- rarely does the syrinx need to be shunted, only when progressive and size allows for insertion of tube

**American Spinal Injury Association Impairment Scale**

| Grade | Description |
|---|---|
| A | Complete, no motor/sensory below neurological level including S4/5 |
| B | Incomplete, sensory but not motor function preserved below neurological level including S4/5 |
| C | Incomplete, motor function preserved below neurological level, and more than half of the key muscles below neurological level have a muscle grade <3 |
| D | Incomplete, motor function preserved below neurological level, and more than half of the key muscles below neurological level have a muscle grade ≥3 |
| E | Normal motor and sensory function |

# Spinal Cord Syndromes

### Complete Spinal Cord Lesion
- bilateral loss of motor/sensory and autonomic function at ≥4 segments below lesion/injury, with UMN signs
- about 3% of patients with complete injuries will develop some recovery within 24 h, beyond 24 h, no distal function will recover

### Incomplete Spinal Cord Lesion
- any residual function at ≥4 segments below lesion
- signs include sensory/motor function in lower limbs and "sacral sparing" (perianal sensation, voluntary rectal sphincter contraction)

**Table 17. Comparison Between Incomplete Spinal Cord Lesion Syndromes**

| Syndrome | Etiology | Motor | Sensory |
|---|---|---|---|
| **Brown-Séquard** | Hemisection of cord | Ipsilateral LMN weakness at the lesion<br>Ipsilateral UMN weakness below the lesion | Ipsilateral loss of vibration and proprioception<br>Contralateral loss of pain and temperature<br>Preserved light touch |
| **Anterior Cord** | Anterior spinal artery compression or occlusion | Bilateral LMN weakness at the lesion<br>Bilateral UMN weakness below the lesion<br>Urinary retention | Preserved vibration and proprioception<br>Bilateral loss of pain and temperature<br>Preserved light touch |
| **Central Cord (most common)** | Syringomyelia, tumours, spinal hyperextention injury | Bilateral motor weakness: Upper limb weakness (LMN lesion) > Lower limb weakness (UMN lesion)<br>Urinary retention | Variable bilateral suspended sensory loss<br>Loss of pain and temperature > loss of vibration and proprioception |
| **Posterior Cord** | Posterior spinal artery infarction, trauma | Preserved | Bilateral loss of vibration, proprioception, light touch at and below the lesion<br>Preserved pain and temperature |

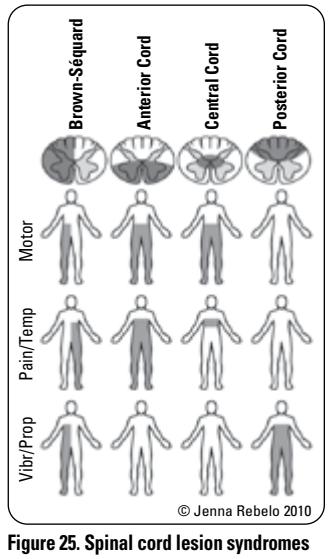



**Figure 25. Spinal cord lesion syndromes**

**Guideline for Timing of Decompressive Surgery in Management of Acute Spinal Cord Injury and Central Cord Syndrome: Results of a Systematic Review**
Global Spine Journal 2017; 7(3S): 195S-202S
**Summary of recommendations:**
- Low quality of evidence: Early surgery (<24 hours after injury) should be considered as a treatment option in adult patients with traumatic central cord syndrome.
- Low quality of evidence: Early surgery should be offered as an option for adult acute SCI patients, regardless of level of lesion.

# Peripheral Nerves

- see Neurology, N36

### Classification

**Table 18. Seddon's Classification of Peripheral Nerve Injury**

| Nerve Injury | Description | Recovery |
|---|---|---|
| **Neurapraxia (class I)** | Axon structurally intact but fails to function | Within hours to months (average 6-8 wk) |
| **Axonotmesis (class II)** | Axon and myelin sheath disrupted but endoneurium and supporting structures intact → Wallerian degeneration of axon segment distal to injury | Spontaneous axonal recovery at 1 mm/d, max at 1-2 yr |
| **Neurotmesis (class III)** | Nerve completely transected | Need surgical repair for possibility of recovery |

### Etiology
- ischemia
- nerve entrapment – nerve compressed by nearby anatomic structures, often secondary to localized, repetitive mechanical trauma with additional vascular injury to nerve
- direct trauma (e.g. transection)
- iatrogenic

### Investigations
- clinical exam: muscle bulk and tone, power, sensation, reflexes, localization via Tinel's sign (paresthesias elicited by tapping along the course of a nerve)
- electrophysiological studies: EMG/nerve conduction study (assess nerve integrity and monitoring recovery after 2-3 wk post-injury)
- labs: blood work (e.g. CBC, TSH, Vitamin B12), CSF
- imaging: C-spine, chest/bone x-rays, myelogram, CT, magnetic resonance neurography, angiogram if vascular damage is suspected

### Treatment
- early neurosurgical consultation if injury is suspected

**Table 19. Treatment by Injury Type**

| Injury | Treatment |
|---|---|
| **Entrapment** | Conservative: Prevent repeated stress/injury, physiotherapy, NSAIDs, local anesthesia/steroid injection<br>Surgical: Nerve decompression ± transposition for progressive deficits, muscle weakness/atrophy, failure of medical management |
| **Stretch/Contusion** | Follow-up clinically for recovery; exploration if no recovery in 3 mo |
| **Axonotmesis** | If no evidence of recovery, resect damaged segment<br>Prompt physical therapy and rehabilitation to increase muscle function, maintain joint ROM, maximize return of useful function<br>Recovery usually incomplete |
| **Neurotmesis** | Surgical repair of nerve sheath unless known to be intact (suture nerve sheaths directly if ends approximate or nerve graft [usually sural nerve])<br>Clean laceration: early exploration and repair<br>Contamination or associated injuries: tag initially with nonabsorbable suture, reapproach within 10 d |

### Complications
- loss of function (temporarily or permanently)
- neuropathic pain: with neuroma formation
- complex regional pain syndrome: with sympathetic nervous system involvement

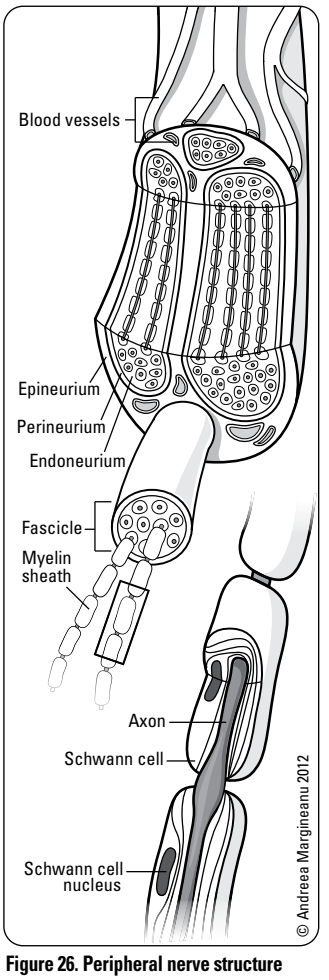



**Figure 26. Peripheral nerve structure**

# SPECIALTY TOPICS

# Neurotrauma

### Trauma Management (see Emergency Medicine, ER7)

### Indications for Intubation in Trauma
1. depressed or decreasing LOC (patient cannot protect airway): usually GCS ≤8
2. need for hyperventilation
3. severe maxillofacial trauma: patency of airway is doubtful
4. need for pharmacologic paralysis for evaluation or management
   - if basal skull fracture suspected, avoid nasotracheal intubation as may inadvertently enter brain
   - note: intubation prevents patient's ability to verbalize for determining GCS

**Glasgow Coma Scale**

| Eye Response | Verbal Response | Motor Response |
|---|---|---|
| 4 spontaneous | 5 oriented | 6 obeys commands |
| 3 opens eyes to voice | 4 confused | 5 localizes to pain |
| 2 opens eyes to pain | 3 inappropriate words | 4 withdraws from pain |
| 1 no eye opening | 2 incomprehensible sounds | 3 flexion to pain (decorticate posturing) |
| | 1 no response | 2 extension to pain (decerebrate posturing) |
| | T intubated | 1 no response |

Best response for each component recorded individually (e.g. E3V3M5)
≥13 is mild injury; 9-12 is moderate injury; ≤8 is severe injury

# Trauma Assessment

### Initial Management

### ABCs of Trauma Management
- see Emergency Medicine, ER2

### NEUROLOGICAL ASSESSMENT

### Mini-History
- period of LOC, post-traumatic amnesia, loss of bowel/bladder control, loss of sensation, weakness, type of injury/accident
- in urgent situations, remember "**SAMPLE-F**": **s**igns/**s**ymptoms, **a**llergies, **m**edications, **p**ast medical history, **l**ast meal, **e**vents leading up to the trauma, and baseline **f**unctioning

### Neurological Exam
- ABCs
- vital signs
- GCS
- brainstem reflexes (if appropriate)
- cranial nerve exam
- motor and sensory exam, including peripheral reflexes
- spine (pain/tenderness, palpable deformity)
- sphincter tone and saddle sensation
- record and repeat neurological exam at regular intervals, as appropriate

### Investigations
- spinal injury precautions (cervical collar) are continued until C-spine is cleared
- C,T,L-spine x-rays
  - AP, lateral, odontoid views for C-spine (must see from C1 to T1; swimmer's view if necessary) or CT
  - rarely done: oblique views looking for pars interarticularis fracture ("Scottie dog" sign)
- CT head and upper C-spine (whole C-spine if patient unconscious) look for fractures, loss of mastoid or sinus air spaces, blood in cisterns, pneumocephalus
- cross and type, ABG, CBC, drug screen (especially alcohol)
- chest and pelvic x-ray as indicated

### TREATMENT

### Treatment for Minor Head Injury (GCS 13-15)
- observation over 24-48 h
- wake every hour
- judicious use of sedatives or pain killers during monitoring period
- outpatient: advise patients to undergo stepwise approach to return to play and return to school (for latest recommendations, refer to Ontario Neurotrauma Foundation guidelines)

### Treatment for Moderate (GCS 9-12) and Severe Head Injury (GCS ≤8)
- clear airway and ensure breathing; intubate if necessary
- secure C-spine
- maintain adequate BP
- monitor for clinical deterioration
- monitor and manage increased ICP if present (see Herniation Syndromes, NS7)

### Admission required if:
- skull fracture (indirect signs of basal skull fracture, see Head Injury)
- confusion, impaired consciousness, concussion with >5 min amnesia
- focal neurological signs, extreme H/A, vomiting, seizures
- unstable spine
- use of alcohol
- poor social support

- Never do LP in head injury unless increased ICP has been ruled out
- All patients with head injury have C-spine injury until proven otherwise
- Suspect hematoma in alcoholic-related injuries
- Low BP after head injury means injury elsewhere
- Must clear spine both radiologically AND clinically

**Assessment of Spine CT/X-Ray (Parasagittal View)**
**ABCDS**
**A**lignment (columns: anterior vertebral line, posterior vertebral line, spinolaminar line, posterior spinous line)
**B**one (vertebral bodies, facets, spinous processes)
**C**artilage
**D**isc (disc space and interspinous space)
**S**oft tissues

**Comparative Effectiveness of Using Computed Tomography Alone to Exclude Cervical Spine Injuries in Obtunded or Intubated Patients: Meta-Analysis of 14,327 Patients with Blunt Trauma**
J Neurosurg 2011;115:541-549
**Purpose**: To determine the effectiveness of helical CT alone (vs. CT and adjuvant imaging such as MR) to diagnose acute unstable cervical spine injury following blunt trauma.
**Results**: 17 studies with 14,327 patients total. Sensitivity and specificity for modern CT were both >99.9% (95% CI 0.99 -1.00 for both). The negative predictive value of a normal CT scan was 100% (95% CI 0.96-1.00) and accuracy was not affected by the global severity of injury, CT slice thickness, or study quality.
**Conclusions**: CT alone is sufficient to detect unstable cervical spine injuries in trauma patients and adjuvant imaging is unnecessary with a negative CT scan result. Consequently, if a CT scan is negative for acute injury, the cervical collar may be removed from obtunded or intubated trauma patients.

## Head Injury

### Epidemiology
- M:F = 2-3:1

### Pathogenesis
- acceleration/deceleration: contusions, subdural hematoma, axon and vessel shearing/mesencephalic hematoma
- impact: skull fracture, concussion, epidural hematoma
- penetrating: worse with high velocity and/or high missile mass
  - low velocity: highest damage to structures on entry/exit path
  - high velocity: highest damage away from missile tract

### Scalp Injury
- rich blood supply
- considerable blood loss (vessels contract poorly when ruptured)
- minimal risk of infection due to rich vascularity

### Skull Fractures
- depressed fractures: double density on skull x-ray (outer table of depressed segment below inner table of skull), CT with bone window is gold standard
- simple fractures (closed injury): no need for antibiotics, no surgery
- compound fractures (open injury): increased risk of infection, surgical debridement within 24 h is necessary
  - internal fractures into sinus may lead to meningitis, pneumocephalus
  - risk of operative bleed may limit treatment to antibiotics

**The Canadian CT Head Rule for Patients with Minor Head Injury**
Lancet 2001;357:1391-1396
**CT Head is only required for patients with minor head injuries with any one of the following:**
**High Risk** (for neurological intervention)
- GCS score <15 at 2 h after injury
- Suspected open or depressed skull fracture
- Any sign of basal skull fracture (hemotympanum, "raccoon" eyes, cerebrospinal fluid otorrhea/rhinorrhoea, Battle's sign)
- Vomiting ≥2 episodes
- Age ≥65 yr

**Medium Risk** (for brain injury on CT)
- Amnesia after impact >30 min.
- Dangerous mechanism (pedestrian struck by motor vehicle, occupant ejected from motor vehicle, fall from height >3 feet or five stairs).

**Minor Head Injury** is defined as witnessed LOC, definite amnesia, or witnessed disorientation in a patient with a GCS score of 13-15.

- basal skull fractures: not readily seen on x-ray, rely on clinical signs
  - retroauricular ecchymoses (Battle's sign)
  - periorbital ecchymoses (raccoon eyes)
  - hemotympanum
  - CSF rhinorrhea, otorrhea (suspect CSF if halo or target sign present); suspect with Lefort II/III midface fracture

### Cranial Nerve Injury
- most traumatic causes of cranial nerve injury do not warrant surgical intervention
- surgical intervention
  - CN II: local eye/orbit injury
  - CN III, IV, VI: if herniation secondary to mass
  - CN VIII: repair of ossicles
- CN injuries that improve
  - CN I: recovery may occur in a few months; most do not improve
  - CN III, IV, VI: majority recover
  - CN VII: recovery with delayed lesions
  - CN VIII: vestibular symptoms improve over weeks, deafness usually permanent (except when resulting from hemotympanum)

### Arterial Injury
- e.g. carotid-cavernous (C-C) fistula, carotid/vertebral artery dissection

### Intracranial Bleeding
- see *Blood*, NS6 and *Cerebrovascular Disease*, NS18

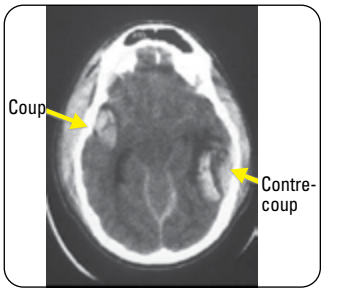



**Figure 27. CT showing coup-contrecoup injury**

## Brain Injury

### Primary Impact Injury
- mechanism of injury determines pathology: penetrating injuries, direct impact
  - low velocity: local damage
  - high velocity: distant damage possible (due to wave of compression), concussion
- concussion: a trauma-induced alteration in mental status
  - refer to American Academy of Neurology (AAN) guidelines for classification and management
  - no parenchymal abnormalities on CT
- coup (damage at site of blow) and contrecoup (damage at opposite site of blow) (Figure 27)
  - acute decompression causes cavitation followed by a wave of acute compression
- contusion (hemorrhagic)
  - high density areas on CT ± mass effect
  - commonly occurs with brain impact on bony prominences (inferior frontal lobe, pole of temporal lobe)
- diffuse axonal injury/shearing
  - wide variety of damage results
  - may tear blood vessels (hemorrhagic foci)
  - often the cause of decreased LOC if no space-occupying lesion on CT

**AAN Classification**
Grade 1: altered mental status <15 min
Grade 2: altered mental status >15 min
Grade 3: any LOC

SIADH → hyponatremia
DI → hypernatremia

**Concussion Grades**

| AAN Grade | Management Options |
|---|---|
| 1 | Examine 15 min for amnesia and other symptoms<br>Return to normal activity if symptoms clear within 15 min |
| 2 | Remove from activity for 1 d, then re-examine<br>CT or MRI if H/A or other symptoms worsen or last >1 wk<br>Return to normal activity after 1 wk without symptoms |
| 3 | Emergent neurological exam and imaging; if initial exam is normal, may go home with close follow-up<br>Admit if any signs of pathology or persistent abnormal mental status<br><br>CT or MRI if H/A or other symptoms<br>If brief LOC (<1 min), return to normal activity after 1 wk without symptoms<br>If prolonged LOC (>1 min), return to normal activity only after 2 wk without symptoms |

### Secondary Pathologic Processes
- same subsequent biochemical pathways for each traumatic etiology
- delayed and progressive injury to the brain due to
  - high glutamate release → NMDA receptor activation → cytotoxic cascade
  - cerebral edema
  - intracranial hemorrhages
  - ischemia/infarction
  - raised ICP, intracranial HTN
  - hydrocephalus

### Extracranial Conditions
- hypoxemia
  - due to trauma to the chest, upper airway, brainstem
  - extremely damaging to vulnerable brain cells
  - leads to ischemia, raised ICP
- hypercarbia
  - leads to raised ICP (secondary to vasodilation)
  - systemic hypotension
  - caused by blood loss (e.g. ruptured spleen)
  - loss of cerebral autoregulation leads to decreased CPP, ischemia
- hyperpyrexia
  - leads to increased brain metabolic demands → ischemia

- fluid and electrolyte imbalance
  - iatrogenic (most common)
  - SIADH caused by head injury
  - DI
  - may lead to cerebral edema and raised ICP
- coagulopathy

### Intracranial Conditions
- raised ICP due to traumatic cerebral edema OR traumatic intracranial hemorrhage

### Brain Injury Outcomes
- mildly traumatic (GCS 13-15): post-concussive symptoms: H/A, fatigue, dizziness, nausea, blurred vision, diplopia, memory impairment, tinnitus, irritability, low concentration; 50% at 6 wk, 14% at 1 yr
- moderately traumatic (GCS 9-12): proportional to age (>40) and CT findings; 60% good recovery, 26% moderately disabled, 7% severely disabled, 7% vegetative/dead
- severe (GCS ≤8): difficult to predict, correlates with post-resuscitation GCS (especially motor) and age

### Late Complications of Head/Brain Injury
- seizures: 5% of head injury patients develop seizures
  - incidence related to severity and location of injury (increased with local brain damage or intracranial hemorrhage)
  - post-traumatic seizure may be immediate, early, or late
  - presence of early (within first wk) post-traumatic seizure raises incidence of late seizures
- meningitis: associated with CSF leak from nose or ear
- hydrocephalus: acute hydrocephalus or delayed NPH
- Post-Concussion Syndrome: H/A, dizziness, cognitive changes, psychological and behavioural symptoms

**A Trial of Intracranial-Pressure Monitoring in Traumatic Brain Injury**
NEJM 2012;367:2471-2481
**Background**: ICP monitoring is frequently used to monitor severe TBI, but controversy exists over whether it is beneficial.
**Methods**: Study sample (n=324 patients, ≥13 yr) consisted of those who had severe TBI and were being treated in ICU in Bolivia or Ecuador. Patients were randomly assigned to one management group:
1. ICP-monitoring based management.
2. Management based on imaging and clinical examination.
Primary outcome was a composite of survival time, impaired consciousness, functional status (at 3, 6 mo), and neuropsychological status (at 6 mo).
**Results**: No significant difference between management groups based on primary outcome, 6 mo mortality, median length of ICU stay, or occurrence of serious adverse events. However, duration of brain-specific treatments (e.g. use of hyperosmolar fluids or hyperventilation) higher in the imaging-clinical examination group (4.8 d vs. 3.4 d, p=0.002).
**Conclusion**: Maintaining monitored ICP at 20 mmHg or less is not superior to care based on imaging and clinical examination.

# Spinal Cord Injury

- see Orthopedic Surgery, OR23 and Emergency Medicine, ER9

### NEUROGENIC AND SPINAL SHOCK
1. neurogenic shock: hypotension that follows SCI (sBP usually ≤80 mmHg) caused by
   - interruption of sympathetics (unopposed parasympathetics) below the level of injury
   - loss of muscle tone due to skeletal muscle paralysis below level of injury → venous pooling (relative hypovolemia)
   - blood loss from associated wounds (true hypovolemia)
2. spinal shock: transient loss of all neurologic function below the level of the SCI, causing flaccid paralysis and areflexia for variable periods

Resolution of spinal shock is indicated by the return of reflexes (most commonly the bulbocavernous reflex)

### Whiplash-Associated Disorders
- definition: traumatic injury to the soft tissue structures in the region of the cervical spine due to hyperflexion, hyperextension, or rotational injury to the neck

### Initial Management of Spinal Cord Injury
- major causes of death in SCI are aspiration and shock
- the following patients should be treated as having a SCI until proven otherwise:
  - all victims of significant trauma
  - minor trauma patients with decreased LOC or complaints of neck or back pain, weakness, abdominal breathing, numbness/tingling, or priapism

**Pharmacological Therapy for Acute Spinal Cord Injury: Congress of Neurological Surgeons (CNS) and American Association of Neurological Surgeons (AANS) Guidelines**
Neurosurgery 2013;72(Suppl 2):93-105
**Level I Recommendations**
- No Class I or Class II medical evidence supports the use of methylprednisone in the treatment of acute SCI. Several Class II and Class III studies have been published stating inconsistent effects of methylprednisone likely related to random chance or selection bias.
- Administration of GM-1 ganglioside (Sygen) for the treatment of acute SCI is not recommended.

### Stabilization and Initial Evaluation in the Hospital
1. ABCs, immobilization (backboard/head strap), oxygenation, Foley catheter to urometer, temperature regulation
2. hypotension: maintain sBP >90 mmHg with pressors (dopamine), hydration, and atropine
   - DVT prophylaxis
3. monitor CBC/electrolytes
4. focused history (see Trauma Assessment, NS30)
5. spine palpation: point tenderness or deformity
6. motor level assessment (including rectal exam for voluntary anal sphincter contraction)
7. sensory level assessment: pinprick, light touch, and proprioception
8. evaluation of reflexes
9. signs of autonomic dysfunction: altered level of perspiration, bowel or bladder incontinence, priapism
10. radiographic evaluation
    - 3 views C-spine x-rays (AP, lateral, and odontoid) to adequately visualize C1 to C7-T1 junction
    - flexion-extension views to disclose occult instability
    - CT scan (bony injuries) typically most trauma centres use CT as the modality of choice for looking at fractures, very sensitive with the high resolution scanners
    - MRI mandatory if neurological deficits (soft tissue injuries)

**Early vs. Delayed Decompression for Traumatic Cervical Spinal Cord Injury: Results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS)**
PLoS ONE 2012;7:e32037. doi:10.1371/journal.pone.0032037
**Introduction**: This study sought to determine the relative effectiveness of early (<24 h after injury) versus late (≥24 h after injury) decompressive surgery following a traumatic cervical SCI.
**Methods/Population**: A prospective cohort study completed in 2002-2009 involving 6 North American institutions. Participants were 16-80 yr with a cervical SCI. Outcomes evaluated were changes in American Spinal Injury Association Impairment Scale (AIS) grade at 6 mo follow-up, complications, and mortality.
**Results**: Of 313 participants enrolled, 182 underwent early surgery and 131 underwent late surgery. 222 participants were available for follow-up at 6 mo. The odds of at least 2 grade AIS improvement were greater for those who had early surgery compared to those with late surgery (OR = 2.83, 95% CI 1.10, 7.28). Mortality was observed for each group during the first 30 d post injury. No statistically significant differences were observed for complications (p=0.21).
**Conclusion**: Early decompression surgery following a SCI is safe and associated with higher AIS improvement at 6 mo following injury.

### Medical Management Specific to Spinal Cord Injury
- option: methylprednisolone (given within 8 h of injury) this is controversial and you need to confer with Neurosurgery service
- ± decompression in acute, non-penetrating SCI

# Fractures of the Spine

## FRACTURES AND FRACTURE-DISLOCATIONS OF THE THORACIC AND LUMBAR SPINE
- assess ligamentous instability using flexion/extension x-ray views ± MRI
- thoracolumbar spine unstable if 4/6 segments disrupted (3 columns divided into left and right)
  - anterior column: anterior half of vertebral body, disc, and anterior longitudinal ligament
  - middle column: posterior half of vertebral body, disc, and posterior longitudinal ligament
  - posterior column: posterior arch, facet joints, pedicle, lamina and supraspinous, interspinous, and ligamentum ligaments

### Types of Injury

**Table 20. Denis Classification of Spinal Trauma**

| Fracture Type | Description |
|---|---|
| **Compression Fracture (58%)** | Produced by flexion<br>Posterior ligament complex (supraspinous and interspinous ligaments, ligamentum flavum, and intervertebral joint capsules) remain intact<br>Fractures are stable but lead to kyphotic deformity |
| **Burst Fracture (17%)** | Stable: anterior and middle columns parted with bone retropulsed nearby<br>Hallmark is pedicle widening on AP x-ray<br>Spinal cord (seen on x-ray and CT); posterior column is uninjured<br>Unstable: same as the stable but with posterior column disruption (usually ligamentous) |
| **Flexion Distraction Injury (6%)** | Hyperflexion and distraction of posterior elements<br>Middle and posterior columns fail in distraction<br>Classic: Chance, horizontal fracture through posterior arch, pedicles, posterior vertebral body<br>Can be purely ligamentous, i.e. through PLL and disc |
| **Fracture-Dislocation (6%)** | Anterior and cranial dislocation of superior vertebral body → 3 column failure<br>Three types: (1) flexion-rotation, (2) flexion-distraction, (3) shear/hyperextension (rare) |

### Management of Thoracolumbar Injury
- severity and management based on thoracolumbar injury classification and severity (TLICS) classification

## FRACTURES OF THE CERVICAL SPINE

### Types of Injury

**Table 21. Fracture Patterns of the Cervical Spine**

| Fracture Type | Description |
|---|---|
| **C1 Vertebral Fracture** (Jefferson fracture) | Vertical compression forces the occipital condyles of the skull down on the C1 vertebra (atlas), pushing the lateral masses of the atlas outward and disrupting the ring of the atlas<br>Also can cause an occipital condylar fracture |
| **Odontoid Fracture** | Causes C1 and odontoid of C2 to move independently of C2 body<br>This occurs because<br>Normally C1 vertebra and odontoid of C2 are a single functional unit<br>Alar and transverse ligaments on posterior aspect of odontoid usually remain intact after injury<br>Patients often report a feeling of instability and present holding their head with their hands<br>Type II fracture the most common |
| **C2 Vertebral Fracture** (hangman fracture) | Bilateral fracture through the pars interarticularis of C2 with subluxation of C2 on C3 (spondylolisthesis of axis)<br>Usually neurologically intact |
| **Clay-Shoveler Fracture** | Avulsion of spinous process, usually C6 or C7 |

### Imaging
- AP spine x-ray (open-mouth and lateral view), CT

### Treatment
- immobilization in cervical collar or halo vest until healing occurs (usually 2-3 mo)
- Type II and III odontoid fractures
- consider surgical fixation for comminution, displacement, or inability to maintain alignment with external immobilization
- confirm stability after recovery with flexion-extension x-rays

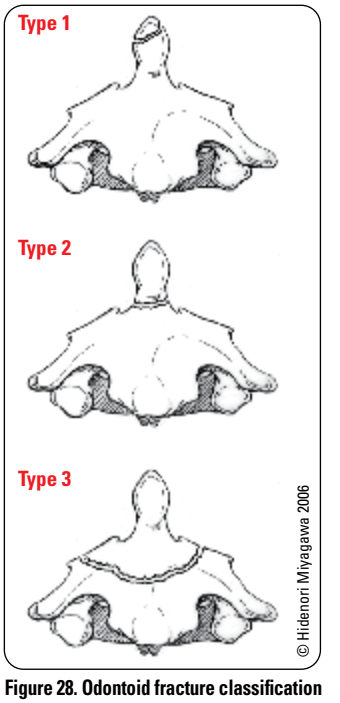


**Figure 28. Odontoid fracture classification**

# Neurologically Determined Death

### Definition
- irreversible and diffuse brain injury resulting in absence of clinical brain function
- cardiovascular activity may persist for up to 2 wk

### Criteria of Diagnosis
- prerequisites: no CNS depressant drugs/neuromuscular blocking agents, no drug intoxication/poisoning, temperature >32°C, no electrolyte/acid-base/endocrine disturbance
- absent brainstem reflexes: pupillary light reflex, corneal reflexes, oculocephalic response, caloric responses (e.g. no deviation of eyes to irrigation of each ear with 50 cc of ice water – allow 1 min after injection, 5 min between sides), pharyngeal and tracheal reflexes, cough with tracheal suctioning, absent respiratory drive at $PaCO_2$ ≥60 mmHg, ≥20 mmHg rise above baseline, and pH ≤7.28 (apnea test)
- 2 evaluations separated by time, usually performed by two specialists (e.g. anesthetist, neurologist, neurosurgeon)
- confirmatory testing: flat EEG, absent perfusion assessed with cerebral angiogram

# Coma

### Definition
- an unrousable state in which patients show no meaningful response to environmental stimuli

### Pathophysiology
- lesions affecting the cerebral cortex bilaterally, the reticular activating system or their connecting fibres
- focal supratentorial lesions do not alter consciousness except by herniation (compression on the brainstem or on the contralateral hemisphere) or by precipitating seizures

### Classification
- structural lesions (tumour, pus, blood, infarction, CSF): 1/3 of comas
  - supratentorial mass lesion: leads to herniation
  - infratentorial lesion: compression of or direct damage to the RAS or its projections
- metabolic disorders/diffuse hemispheric damage: 2/3 of comas
  - deficiency of essential substrates (e.g. oxygen, glucose, vitamin B12)
  - exogenous toxins (e.g. drugs, heavy metals, solvents)
  - endogenous toxins/systemic metabolic diseases (e.g. uremia, hepatic encephalopathy, electrolyte imbalances, thyroid storm)
  - infections (meningitis, encephalitis)
  - trauma (concussion, diffuse shear axonal damage)

### Investigations and Management
- ABCs
- labs: electrolytes, extended electrolytes, TSH, LFTs, Cr, BUN, toxin screen, glucose
- CT/MRI, LP (after ruling out space-occupying lesion/increased ICP), EEG

# Persistent Vegetative State

### Definition
- a condition of complete unawareness of the self and the environment accompanied by sleep-wake cycles with either complete or partial preservation of hypothalamic and brainstem autonomic function
- "awake but not aware"
- follows comatose state

### Etiology/Prognosis
- most commonly caused by cardiac arrest or head injury
- due to irreversible loss of cerebral cortical function but intact brainstem function
- average life expectancy is 2-5 yr

# Pediatric Neurosurgery

## Spinal Dysraphism

- spinal dysraphism refers to a spectrum of congenital anomalies resulting in a defective neural arch through which CNS elements are herniated
- the spectrum is divided largely into aperta (visible lesion; no skin covering) and occulta (no visible lesion; skin covering)

**Thoracolumbar Injury Classification and Severity Scoring**

| Parameter | Points |
|---|---|
| **Morphology** | |
| Compression fracture | 1 |
| Burst fracture | 2 |
| Translational/rotational fracture | 3 |
| Distraction | 4 |
| **Neurologic Status** | |
| Intact | 0 |
| Nerve root injury | 2 |
| **Spinal Cord Status** | |
| Incomplete | 3 |
| Complete | 2 |
| Cauda equine | 3 |
| **Posterior Ligamentous Complex** | |
| Intact | 0 |
| Injury suspected/indeterminate | 2 |
| Injured | 3 |

- TLICS scoring based on morphology of injury, status of posterior ligamentous complex, and neurological status
- Non-operative management if TLICS = 0-3, operative management if TLICS = 5+, either operative or non-operative if TLICS = 4

**Prenatal vs. Postnatal Repair of Myelomeningocele (MMC)**
NEJM 2011; 364:993-1004
**Methods**: RCT comparing prenatal surgery (before 26 weeks of gestation) and standard postoperative surgery. 12 mo outcomes included, death or need for placement of a CSF shunt. 30 mo outcomes included mental development and motor function.
**Results**: 40% of prenatal-surgery patients, compared to 82% of postnatal-surgery patients, required CSF shunt (P<0.001). Prenatal surgery resulted in improvement in mental development and motor function (P=0.007). However, prenatal surgery was associated with an increased risk of gynecological complications.
**Conclusion**: Prenatal surgery for MMC reduced need for shunting and improved motor outcomes but was associated with maternal and fetal risks related to preterm delivery.

**Table 22. Summary of Spinal Dysraphic Anomalies**

| | SPINA BIFIDA OCCULTA | MENINGOCELE (SPINA BIFIDA APERTA) | MYELOMENINGOCELE (SPINA BIFIDA APERTA) |
|---|---|---|---|
| **Definition** | Congenital absence of a spinous process and a variable amount of lamina<br>No visible exposure of meninges or neural tissue | Herniation of meningeal tissue and CSF through a defect in the spine, without associated herniation of neural tissue | Herniation of meningeal and CNS tissue through a defect in the spine |
| **Epidemiology** | 15-20% of the general population; most common at L5 or S1 | 0.1-0.2% of live births | 0.1-0.2% of live births |
| **Etiology** | | Failure of fusion of posterior neural arch | Primary failure of neural tube closure |
| **Clinical Features** | No obvious clinical signs<br>Presence of lumbosacral cutaneous abnormalities (dimple, sinus, port-wine stain, or hair tuft) should increase suspicion of an underlying anomaly (lipoma, dermoid, diastematomyelia) | Most common in lumbosacral area<br>Usually no disability, low incidence of associated anomalies, and hydrocephalus | Sensory and motor changes distal to anatomic level producing varying degrees of weakness<br>Urinary and fecal incontinence<br>Hydrocephalus (65-85% of patients)<br>Most have Type II Chiari malformation (see *Chiari Malformations*) |
| **Investigations** | Plain film: Absence of the spinous process and minor amounts of the neural arch<br>U/S, MRI to exclude spinal anomalies | Plain films, CT, MRI, U/S, echo, GU investigations | Plain films, CT, MRI, U/S, echo, GU investigations |
| **Treatment** | Requires no treatment | Surgical excision and tissue repair | Surgical closure to preserve neurologic status and prevent CNS infections<br>Closure *in utero* shown to decrease hydrocephalus and improve post natal motor scores |
| **Prognosis** | Generally good prognosis | Good prognosis with surgical treatment | Operative mortality close to 0%, 95% 2-yr survival<br>80% have IQ >80 (but most are 80-95), 40-85% ambulatory, 3-10% have normal urinary continence<br>Early mortality: usually due to Chiari malformation complications (respiratory arrest, aspiration), late mortality: due to shunt malfunction |

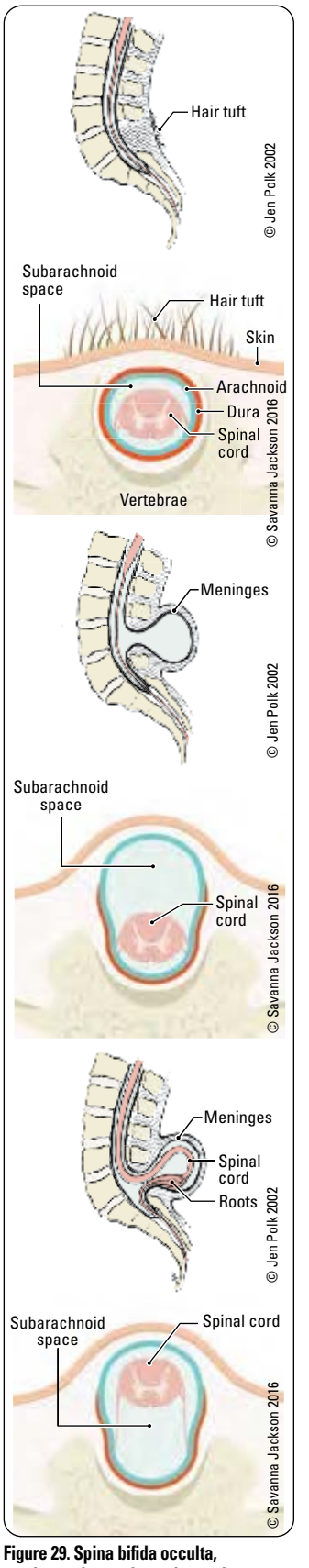



**Figure 29. Spina bifida occulta, meningocele, myelomeningocele**

# Intraventricular Hemorrhage

## Definition
- hemorrhage originating in the periventricular subependymal germinal matrix

## Epidemiology
- incidence and severity increases as GA and BW decrease
- 50% of IVH occurs within 8 h of birth; 90% occurs by day 3

## Risk Factors
- prematurity (<32 wk), BW <1500 g, need for vigorous resuscitation at birth, pneumothorax, ventilated preterm infants, hemodynamic instability, RDS, chorioamnionitis, coagulopathy

## Clinical Feature
- many infants with IVH are asymptomatic
- subtle signs: altered LOC, decreased tone and/or activity, hypoventilation/apnea
- catastrophic deterioration: may have bulging fontanelle, apnea/hypoventilation, hypotension, bradycardia, cranial nerve abnormalities, sudden drop in hematocrit, metabolic acidosis, seizures, coma

## Diagnosis
- head U/S is preferred imaging modality
- routine head U/S screening conducted for all preterm infants <32 wk or <1500 g gestation throughout NICU stay
- IVH graded using Papile classification
- parenchymal hemorrhage may also occur in the absence of IVH

## Management of Acute Hemorrhage
- supportive care to maintain blood volume, cerebral perfusion, and acid-base status
- follow-up with serial imaging

### Prognosis
- outcome largely dependent on grade of IVH, with grades I and II having a relatively favourable prognosis
- greatest morbidity and mortality is seen with grade IV IVH and development of posthemorrhagic hydrocephalus requiring ventriculoperitoneal shunt placement
- short-term sequelae for severe IVH: mortality, extension of bleed, posthemorrhagic hydrocephalus, posthemorrhagic infarction, cyst formation
- possible long-term major neurological sequelae: CP, cognitive deficits, motor deficits, visual and hearing impairment

**Papile Classification**
Grade I: germinal matrix hemorrhage
Grade II: IVH without ventricular dilatation
Grade III: IVH with ventricular dilatation
Grade IV: IVH with parenchymal extension

## Hydrocephalus in Pediatrics

### Etiology
- congenital
  - aqueductal anomalies, primary aqueductal stenosis in infancy
  - secondary gliosis due to intrauterine viral infections (mumps, varicella, TORCH)
  - Dandy-Walker malformation (2-4%)
  - Chiari malformation, especially Type II
  - myelomeningocele
- acquired
  - post meningitis
  - post hemorrhage (SAH, IVH)
  - masses (vascular malformation, neoplastic)

### Clinical Features
- symptoms and signs of hydrocephalus are age related in pediatrics
- increased head circumference, bulging anterior fontanelle, widened cranial sutures
- irritability, lethargy, poor feeding, and vomiting
- "cracked pot" sound on cranial percussion
- scalp vein dilation (increased collateral venous drainage)
- sunset sign (forced downward deviation of eyes)
- episodic bradycardia and apnea

### Investigations
- skull x-ray, U/S, CT, MRI, ICP monitoring

### Treatment
- similar to adults (see *Hydrocephalus Treatment*, NS9)

## Dandy-Walker Malformation

### Definition
- atresia of foramina of Magendie and Luschka, resulting in:
  - complete or incomplete agenesis of the cerebellar vermis with widely separated, hypoplastic cerebellar hemispheres
  - posterior fossa cyst, enlarged posterior fossa
  - dilatation of 4th ventricle (also 3rd and lateral ventricles)
  - can be detected *in utero*
- associated anomalies
  - hydrocephalus (90%)
  - agenesis of corpus callosum (17%)
  - occipital encephalocele (7%)

### Epidemiology
- 2-4% of pediatric hydrocephalus

### Clinical Features
- 20% are asymptomatic, seizures occur in 15%
- symptoms and signs of hydrocephalus combined with a prominent occiput in infancy
- ataxia, spasticity, poor fine motor control common in childhood

### Investigations
- ultrasound, CT, MRI

### Treatment
- asymptomatic patients require no treatment
- associated hydrocephalus requires surgical treatment
  - e.g. ventriculoperitoneal shunt, cystoperitoneal shunt, lumboperitoneal shunt, ventriculoatrial shunt, lumbar drain

### Prognosis
- 75-100% survival, 50% have normal IQ

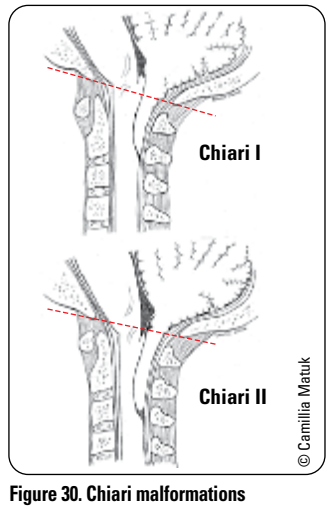


**Figure 30. Chiari malformations**

# Chiari Malformations

## Definition
- malformations at the medullary-spinal junction

## Etiology
- unclear, likely maldevelopment/dysgenesis during fetal life

## Categories

**Table 23. Categories of Chiari Malformations**

| | Type I | Type II |
|---|---|---|
| **Definition** | Cerebellar tonsils lie below the level of the foramen magnum | Part of cerebellar vermis, medulla, and 4th ventricle extend through the foramen magnum often to midcervical region |
| **Epidemiology** | Average age at presentation 15 yr | Present in infancy |
| **Clinical Features** | Many are aysmptomatic<br>Pain (69%), weakness (56%), numbness (52%), loss of temperature sensation (40%)<br>Central cord syndrome (65%)<br>Foramen magnum compression syndrome (22%), Cerebellar syndrome (11%), Syringomyelia (50%), Hydrocephalus (10%) | Findings due to brainstem and lower cranial nerve dysfunction<br>Neurogenic dysphagia (69%), apnea (58%), stridor (56%), aspiration (40%), arm weakness (27%), downbeat nystagmus<br>Respiratory arrest is the most common cause of mortality<br>Usually associated with myelomingocele and hydrocephalus |
| **Investigations** | MRI | MRI |
| **Treatment** | Symptomatic patients (early surgery recommended; <2 yr post symptom onset) → suboccipital craniectomy, duraplasty | Preserved<br>When symptomatic, check the shunt first. Then consider surgical decompression (which does not reverse intrinsic brainstem abnormalities) → cervical laminectomy, duraplasty |

# Craniosynostosis

## Definition
- premature closure of the cranial suture(s)

## Classification
- sagittal (most common): long narrow head with ridging sagittal suture (scaphocephaly)
- coronal: expansion in superior and lateral direction (brachiocephaly)
- metopic (trigonocephaly)
- lambdoid: least common

## Epidemiology
- 0.6/1000 live births, most cases are sporadic; familial incidence is 2% of sagittal and 8% of coronal synostosis

## Clinical Features
- skull deformity, raised ICP ± hydrocephalus
- ophthalmologic problems due to increased ICP or bony abnormalities of the orbit
- must differentiate from positional plagiocephaly (secondary to persistently/exclusively sleeping on back)

## Investigations
- plain radiographs, CT scan

## Treatment
- parental counselling about nature of deformity, associated neurological symptoms
- surgery for cosmetic purposes, except in cases of elevated ICP (≥2 sutures involved)

# Pediatric Brain Tumours

- see *Tumours*, NS11

**Most Common Pediatric Brain Tumours**
Astrocytoma, low grade
Supratentorial
Infratentorial
Medulloblastoma
Ependymoma
Glioblastoma

## Epidemiology
- 20% of all pediatric cancers (second only to leukemia)
- 60% of pediatric brain tumours are infratentorial
- pediatric brain tumours arise from various cellular lineages
- glia: low-grade astrocytoma (supra- or infratentorial), anaplastic astrocytoma, glioblastoma multiforme (largely supratentorial) (see *Astrocytoma*, NS13)
- primitive nerve cells: supratentorial PNET
- 90% of neonatal brain tumours, infratentorial (medulloblastoma), pineal gland (pineoblastoma)
- non-neuronal cells: germ cell tumour, craniopharyngioma, dermoid, meningioma, neurinoma (schwanoma), pituitary adenoma, others

## Clinical Features
- vomiting, seizure, macrocrania, hydrocephalus
- developmental delay, poor feeding, failure to thrive
- often initially escapes diagnosis due to expansile cranium and neural plasticity in children

**Table 24. Overview of Childhood Primary Brain Tumours***

| | |
|---|---|
| **Pilocytic (low grade) Astrocytoma** | Usually in posterior fossa<br>Well circumscribed<br>Benign, good prognosis |
| **Medulloblastoma** | PNET<br>In cerebellum → compresses 4th ventricle → hydrocephalus<br>Highly malignant |
| **Ependymoma** | In 4th ventricle → hydrocephalus<br>Poor prognosis |
| **Hemangioblastoma** | Often cerebellar<br>Associated with von Hippel-Lindau syndrome with retinal angiomas<br>Can produce EPO → secondary polycythemia |
| **Craniopharyngioma** | Causes bitemporal hemianopsia (thus often confused with pituitary adenoma)<br>Most common supratentorial childhood tumour<br>Benign |

* See also, *Familial Cancer Syndromes*, Medical Genetics, MG7

# Functional Neurosurgery

## Movement Disorders

- see Neurology, *Parkinson's Disease*, N32, *Dystonia*, N33, and *Multiple Sclerosis*, N52

**Table 25. Surgical Targets for Movement Disorders**

| Disorder | Indications | Procedures | Outcomes | Morbidity |
|---|---|---|---|---|
| **Parkinson's Disease** | Intractable contralateral bradykinesia/tremor<br>Failure of medical management (advanced disease)<br>Drug-induced dyskinesias (see dystonia, below) | Simultaneous, bilateral surgery/stimulation is most common<br>Preferred target: Anterodorsal subthalamic nucleus<br>Other targets: stereotactic ablation (pallidotomy) or stimulation of posteroventral GPi<br>Caudal zona incerta<br>Parkinsonian tremor: stereotactic ablation (thalamotomy) or stimulation of ventral intermediate nucleus of thalamus | 39-48% improvement in Unified Parkinson's Disease Rating Scale (UPDRS) scores<br>Reduced dosage of medications (STN)<br>More effective than medical management in advanced PD<br>Early intervention may reduce severity, course, and progression of disease<br>Less effective for patients with atypical presentations | IH, infection, seizure (1%-4%)<br>Paresthesias<br>Involuntary movements<br>Cognitive functioning: Decreased lexical fluency, impaired executive function (STN > GPi)<br>Psychiatric: Depression, mania, anxiety, apathy (STN > GPi) |
| **Dystonia** | Contralateral primary (generalized) dystonias; cervical and tardive dystonias<br>Contralateral secondary dyskinesia (i.e. drug-induced: L-dopa, neuroleptics) | Preferred target (primary dystonia): Stereotactic ablation (pallidotomy) or stimulation of posteroventral GPi<br>Secondary dystonia: stimulation of anterodorsal STN<br>Stimulation of ventral posterior lateral (VPL) thalamic nucleus | Primary dystonia: 51% reduction in Burke-Fahn-Marsden Dystonia Scale (BFMDS) score<br>Secondary dystonia: 62-89% improvement in dystonias<br>Delayed effects: Weeks to months | ICH, infection, seizure (1%-4%)<br>Minor effects on cognitive functioning (especially decreased lexical fluency; STN > GPi) |
| **Tremor** | Contralateral appendicular ET (first disorder to be treated by DBS; DBS is viable alternative to Rx)<br>Intention tremor resulting from demyelination of cerebellar outflow tracts (e.g. in multiple sclerosis)<br>Brainstem tremor (Holmes tremor) | Preferred target: Stereotactic ablation (thalamotomy) or stimulation of Vim nucleus of thalamus<br>Other targets: stimulation of caudal zona incerta<br>Parkinsonian tremor: stimulation of anterodorsal STN | Durable reductions in essential tremor rating scale (ETRS) scores<br>Reduced dosage of medications<br>Conflicting data on vocal/facial tremor | ICH, infection, seizure (1%-4%)<br>Paresthesias/pain<br>Dysarthria<br>Ataxia<br>Minor effects on cognitive functioning (especially decreased lexical fluency)<br>Tolerance may develop over time |

# Neuropsychiatric Disorders

- see Neurology, N20 and *Obsessive Compulsive Disorder* PS19 and *Depression*, PS12
- psychiatric neurosurgery indicated only for severe symptoms that are refractory to medical management

**Table 26. Surgical Targets for Neuropsychiatric Disorders**

| Disorder | Procedures | Outcomes | Morbidity |
|---|---|---|---|
| **Obsessive Compulsive Disorder (OCD)** | Anterior capsulotomy/stimulation of the anterior limb of the internal capsule (IC) | Currently under investigation<br>Reportedly 25-75% response rate | ICH (1-2%)<br>Mild effects on cognitive functioning<br>Anxiety ± panic disorder (case report) |
| **Tourette's Syndrome** | Stimulation of midline intralaminar nuclei of the thalamus<br>Stimulation of motor and limbic portions of GPi<br>Stimulation of the anterior limb of the IC | Currently under investigation<br>Reportedly >70% reduction in vocal or motor tics and urge | Intracerebral hemorrhages (1-2%)<br>Mild sexual dysfunction |
| **Major Depressive Disorder (MDD)** | Stimulation of the subgenual cingulate cortex<br>Anterior capsulotomy or stimulation of the anterior limb of the internal capsule (IC) | Currently under investigation<br>Reportedly 60% response rate; 35% remission rate | ICH (1-2%)<br>Pain, H/A<br>Worsening mood, irritability |

**Consensus on Guidelines for Stereotactic Neurosurgery for Psychiatric Disorders**
Journal of Neurology, Neurosurgery & Psychiatry 2014;85(9): 1003-1008

- Stereotactic ablative procedures such as cingulotomy and capsulotomy for MDD and OCD lack level I evidence.
- Deep brain stimulation in any brain target attempted so far is considered "investigational."
- Multidisciplinary teams are mandatory to ensure safe and ethical conduct in psychiatric neurosurgery, with particular attention directed to ensuring treatment refractoriness, consent procedures, patient capacity and autonomy, and extensive pre-/post- operative assessments.

- other experimental indications include: anorexia nervosa, substance use disorders, Tourette's syndrome, and functional neurological disorders, amongst others

# Chronic Pain

**Table 27. Surgical Targets for Chronic Pain**

| Disorder | Indications | Procedures | Outcomes | Morbidity |
|---|---|---|---|---|
| **Neuropathic Pain** | Severe, intractable, organic neuropathic pain (e.g. post-stroke pain, phantom limb pain, trigeminal neuralgia, chronic low-back pain, post-operative neuropathic pain, complex regional pain syndrome) | Preferred target: stimulation of the contralateral VPL<br>VPM thalamic nuclei ± periventricular/periaqueductal grey matter (PVG/PAG)<br>Other targets: stimulation of the contralateral IC<br>Stimulation of the contralateral motor cortex<br><br>For post-operative neuropathic pain, surgical procedure may be aimed at correcting any identifiable residual deformity from prior spine surgery<br>Surgery is not primary modality if no structurally correctable radiologic findings | 47% improvement in perception of pain intensity<br>Less favourable results in central pain syndromes and poorly localized pain | Intracerebral hemorrhages (1-2%)<br>Paresthesia<br>Anxiety ± panic disorder |
| **Nociceptive Pain** | Severe, intractable, organic nociceptive pain | Bilateral (most common) stimulation of the PVG/PAG | Reportedly 63% improvement in perception of pain intensity | Intracerebral hemorrhages (1-2%)<br>Paresthesia<br>Anxiety ± panic disorder |

# Surgical Management of Epilepsy

- see Neurology, N18 for the medical treatment of epilepsy

## Indications

- medically refractory seizures, usually defined as recurrent seizures resistant to two first line anti-seizure medications used in succession
- identification of a distinct epileptogenic region through clinical history, EEG, MRI, and neuropsychological testing; other localizing investigations include magnetoencephalography, SPECT, and PET
- if a distinct epileptogenic region cannot be identified, the patient may be a candidate for a palliative procedure such as corpus callosotomy

### Procedure
- adults: resection of the hippocampus and parahippocampal gyrus for mesial temporal lobe epilepsy arising from mesial temporal sclerosis
- children: resection of an epileptogenic space-occupying lesion
- hemispherectomy and corpus callosotomy are less common
- vagus nerve stimulation
- deep brain stimulation

### Outcomes
- 41-79% of adult patients are seizure free for 5 yr after temporal lobe resection
- 58-78% of children are seizure free after surgery
- surgery is associated with improvements in preexisting psychiatric conditions such as depression and anxiety, as well as improvement in quality of life measures

### Morbidity
- 0.4-4% of surgical patients will have partial hemianopsia, aphasia, motor deficit, sensory deficit, or cranial nerve palsy following anteromedial temporal lobectomies
- most patients will have some decline in verbal memory following dominant temporal lobectomy and in visuospatial memory in non-dominant temporal resection
- the degree of memory decline stabilizes after 1-2 yr

### Predictors
- positive predictive factors for seizure freedom following anteromedial temporal lobectomy include:
  - hippocampal sclerosis (unilateral)
  - focal localization of interictal epileptiform discharges
  - absence of pre-operative generalized seizures
  - tumoural etiology
  - complete resection of the lesion
- ongoing research on neuroimaging biomarkers to predict treatment response, especially to neuromodulation

## Surgical Management for Trigeminal Neuralgia

- reserved for cases refractory to medical management; see Neurology, N42 for medical management

### Surgical Options
- trigeminal nerve branch procedures
  - local blocks (phenol, alcohol)
  - neurectomy of the trigeminal branch
  - nerve branches
  - V1 block at the supraorbital, supratrochlear nerves
  - V2 block at the foramen rotundum or infraorbital nerves
  - V3 block at the foramen ovale
- percutaneous trigeminal rhizotomy
  - glycerol injection
  - mechanotrauma via catheter balloon
- radiofrequency thermocoagulation
- Gamma Knife® radiosurgery
- microvascular decompression
  - posterior fossa craniotomy with microsurgical exploration of the root entry zone, displacement of the vessel impinging on the nerve with placement of non-absorbable Teflon® felt

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# OB Obstetrics

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# Acronyms

| | |
|---|---|
| AC | abdominal circumference |
| ACOG | American College of Obstetricians and Gynecologists |
| AFI | amniotic fluid index |
| AFLP | acute fatty liver of pregnancy |
| AFV | amniotic fluid volume |
| AP | anteroposterior |
| APGAR | Appearance, pulse, grimace, activity, and respiration |
| aPTT | activated partial thromboplastin time |
| APS | antiphospholipid antibody syndrome |
| ARDS | acute respiratory distress syndrome |
| β-hCG | beta human chorionic gonadotropin |
| BPP | biophysical profile |
| C/S | Cesarean section |
| CHF | congestive heart failure |
| CMV | cytomegalovirus |
| CPD | cephalopelvic disproportion |
| CT | computed tomography scan |
| CTG | cardiotocography |
| CVS | chorionic villus sampling |
| CXR | chest X-ray |
| D&C | dilatation and curettage |
| DIC | disseminated intravascular coagulation |
| DM | diabetes mellitus |
| DVT | deep vein thrombosis |
| ECV | external cephalic version |
| EDD | estimated date of delivery |
| EFM | electronic fetal monitoring |
| eFTS | enhanced first trimester screen |
| EFW | estimated fetal weight |
| FDP | fibrin degradation products |
| FHR | fetal heart rate |
| FISH | fluorescence in situ hybridization |
| FL | femur length |
| FM | fetal movement |
| FPG | fasting plasma glucose |
| FTS | first trimester screen |
| GA | gestational age |
| GBS | Group B *Streptococcus* |
| GDM | gestational diabetes mellitus |
| GTN | gestational trophoblastic neoplasia |
| HC | head circumference |
| HELLP | hemolysis, elevated liver enzymes, low platelets |
| IMM | intramyometrial |
| IOL | induction of labour |
| IPS | integrated prenatal screen |
| ITP | idiopathic thrombocytopenic purpura |
| IUFD | intrauterine fetal death |
| IUGR | intrauterine growth restriction |
| IVH | intraventricular hemorrhage |
| L/S | lecithin-sphingomyelin ratio |
| LFT | liver function test |
| LLDP | left lateral decubitus position |
| LMP | last menstrual period |
| LMWH | low molecular weight heparin |
| MSAFP | maternal serum α-fetoprotein |
| MSS | maternal serum screening |
| MTX | methotrexate |
| N/V | nausea/vomiting |
| NIPT | non-invasive prenatal testing |
| NPO | nothing by mouth |
| NST | non-stress test |
| NTD | neural tube defects |
| NTUS | nuchal translucency ultrasound |
| OA | occiput anterior |
| OGCT | oral glucose challenge test |
| OGTT | oral glucose tolerance test |
| ONTD | open neural tube defect |
| OP | occiput posterior |
| OT | occiput transverse |
| PAPP-A | pregnancy-associated plasma protein A |
| PCR | polymerase chain reaction |
| PE | pulmonary embolism |
| PG | plasma glucose |
| PPD | postpartum depression |
| PPH | postpartum hemorrhage |
| PPROM | preterm premature rupture of membranes |
| PROM | premature rupture of membranes |
| PTL | preterm labour |
| QF-PCR | quantitative fluorescence-polymerase chain reaction |
| RDS | respiratory distress syndrome |
| RhIG | Rh immune globulin |
| ROM | rupture of membranes |
| SFH | symphysis fundal height |
| SOGC | Society of Obstetricians and Gynaecologists of Canada |
| SVD | spontaneous vaginal delivery |
| TENS | transcutaneous electrical nerve stimulation |
| TOLAC | trial of labour after Cesarean section |
| T1 | first trimester |
| T2 | second trimester |
| T3 | third trimester |
| TB | tuberculosis |
| TPN | total parenteral nutrition |
| TTP | thrombotic thrombocytopenic purpura |
| U/S | ultrasound |
| UTI | urinary tract infection |
| V/Q | ventilation/perfusion lung scan |
| VBAC | vaginal birth after Cesarean |
| vWD | von Willebrand disease |
| VTE | venous thromboembolism |

# Basic Anatomy Review

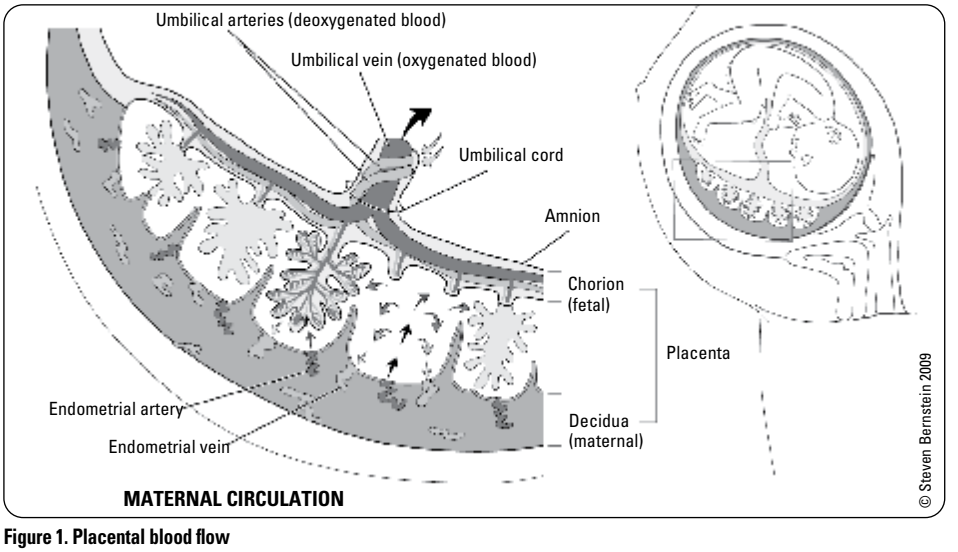



**Figure 1. Placental blood flow**

### Placenta

- site of fetal nutritive, respiratory, and excretory function
- discoid mass composed of fetal (chorion frondosum) and maternal (decidua basalis) tissues divided by fissures into cotyledons (lobules) on the uterine side
- produces hormones such as progesterone, placental lactogen, estrogen, relaxin, β-hCG, and infant growth factors
- poor implantation can lead to spontaneous abortion
- abnormal location, implantation, or detachment can lead to antepartum hemorrhage (see *Obstetrical Hemorrhage*, OB13)

# Pregnancy

## Diagnosis of Pregnancy

### History

- symptoms: amenorrhea, nausea and/or vomiting, breast tenderness, urinary frequency, and fatigue
- obstetrical and gynecological history: year, location, mode of delivery, duration of labour, sex, gestational age, birth weight, and complications of every pregnancy; organize into GTPAL format
  - Gravidity (G)
    - **G**: total number of pregnancies of any gestation (multiple gestation=one pregnancy)
    - includes current pregnancy, abortions, ectopic pregnancies, and hydatidiform moles

- Parity (TPAL)
  - **T**: number of term deliveries (>37 wk)
  - **P**: number of premature deliveries (20-36+6 wk)
  - **A**: number of abortions (ending <20 wk)
    - induced (therapeutic) and spontaneous (miscarriage)
  - **L**: number of living children

### Physical Signs
- uterine enlargement
- breast engorgement, areola darkening, and prominent vascular patterns
- Goodell's sign: softening of the cervix (4-6 wk)
- Chadwick's sign: bluish discolouration of the cervix and vagina due to pelvic vasculature engorgement (6 wk)
- Hegar's sign: softening of the cervical isthmus (6-8 wk)

### Investigations
- β-hCG: peptide hormone composed of α and β subunits produced by placental trophoblastic cells – maintains the corpus luteum during pregnancy
  - positive in serum 9 d post-conception, positive in urine 28 d after 1st day of LMP
  - plasma levels usually double every 1.4-2.0 d, peak at 8-12 wk, then fall, but continue to be measurable until delivery
- levels less than expected suggest ectopic pregnancy, abortion, inaccurate dates, or some normal pregnancies
- levels greater than expected suggest: multiple gestation, molar pregnancy, Trisomy 21, or inaccurate dates
- U/S:
  - transvaginal
    - 5 wk GA: gestational sac visible
    - 6 wk GA: fetal pole visible
    - 7-8 wk GA: fetal heart activity visible
  - transabdominal
    - 6-8 wk GA: intrauterine pregnancy visible



**β-hCG Rule of 10s**
10 IU at time of missed menses
100,000 IU at 10 wk (peak)
10,000 IU at term



**Trimesters**
- T1 (first trimester): 1-14 wk
- T2 (second trimester): 14-28 wk
- T3 (third trimester): 28-42 wk
- Normal pregnancy term: 37-42 wk

# Maternal Physiologic Adaptations to Pregnancy

**Table 1. Physiologic Changes During Pregnancy**

| | |
|---|---|
| **Skin** | Increased pigmentation of perineum and areola, chloasma (pigmentation changes under eyes and on bridge of nose), linea nigra (midline abdominal pigmentation), spider angiomas, palmar erythema due to increased estrogen, and striae gravidarum due to connective tissue changes |
| **Cardiovascular** | Hyper-dynamic circulation<br>Increased cardiac output, heart rate, and blood volume<br>Decreased blood pressure: decreased PVR and decreased venous return from enlarging uterus compressing IVC and pelvic veins<br>Increased venous pressure leads to risk of varicose veins, hemorrhoids, and leg edema |
| **Hematologic** | Hemodilution causes physiologic anemia and apparent decrease in hemoglobin and hematocrit<br>Increased leukocyte count but impaired function leads to improvement in some autoimmune diseases<br>Gestational thrombocytopenia: mild (platelets >70,000/μL) and asymptomatic, normalizes within 2-12 wk following delivery<br>Hypercoagulable state: increased risk of DVT and PE but also decreased bleeding at delivery |
| **Respiratory** | Increased incidence of nasal congestion<br>Increased $O_2$ consumption to meet increased metabolic requirements<br>Elevated diaphragm (i.e. appears more "barrel-chested")<br>Increased minute ventilation leads to decreased $CO_2$ resulting in mild respiratory alkalosis that helps $CO^2$ diffuse across the placenta from fetal to maternal circulation<br>Decreased total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV)<br>No change in vital capacity (VC) and $FEV_1$ |
| **Gastrointestinal** | GERD due to increased intra-abdominal pressure and progesterone (causing decreased sphincter tone and delayed gastric emptying)<br>Increased incidence of gallstones due to progesterone causing increased gallbladder stasis<br>Constipation due to progesterone causing decreased GI motility and hemorrhoids as a result of constipation and increased intra-abdominal pressure |
| **Genitourinary** | Increased urinary frequency due to increased total urinary output<br>Increased incidence of UTI and pyelonephritis due to urinary stasis (see *Urinary Tract Infection*, OB29)<br>Glycosuria that can be physiologic especially in the T3; consider testing for GDM if noted in first 2 trimesters<br>Ureters and renal pelvis dilation (R>L) due to progesterone-induced smooth muscle relaxation and uterine enlargement<br>Increased CO and thus increased GFR leads to decreased creatinine (normal in pregnancy 35-44 mmol/L), uric acid, and BUN |
| **Neurologic** | Increased incidence of carpal tunnel syndrome and Bell's palsy |
| **Endocrine** | Thyroid: moderate enlargement (not clinically detectable) and increased basal metabolic rate<br>Increased total thyroxine and thyroxine binding globulin (TBG)<br>Normal free thyroxine index and FSH levels<br>Adrenal: increased maternal cortisol throughout pregnancy (total and free)<br>Calcium: decreased total maternal $Ca^{2+}$ due to decreased albumin<br>Free ionized $Ca^{2+}$ (i.e. active) proportion remains the same due to parathyroid hormone (PTH), resulting in increased bone resorption and gut absorption, and increased bone turnover (but no loss of bone density due to estrogen inhibition) (see *Diabetes Mellitus*, OB26) |

PVR – pulmonary vascular resistance; $FEV_1$ – forced expiratory volume in 1 second; CO – cardiac output; GFR – glomerular filtration rate; BUN – blood urea nitrogen

# Antepartum Care

- can be provided by an obstetrician, family physician, midwife, or multidisciplinary team (based on patient preference and risk factors)

### Preconception Counselling

- 3-8 wk GA is a critical period of organogenesis, so early preparation is vital
- **past medical history**: optimize medical conditions and review medications prior to pregnancy (see *Medical Complications of Pregnancy*, OB26, and *Medications*, OB49)
- supplementation
  - folic acid: encourage diet rich in folic acid and consider supplementation from 8-12 wk pre-conception until end of T1 to prevent NTD
    - 0.4-1 mg daily in all women; 5 mg if previous NTD, antiepileptic medications, DM, or BMI >35 kg/m$^2$
  - iron supplementation (in cases of iron deficiency anemia), prenatal vitamins
- **risk modification**
  - lifestyle/social: smoking, alcohol, drug use, domestic violence, occupational risks, poor social support, balanced nutrition, and physical fitness (see Family Medicine)
  - medications: discuss teratogenicity of medications so they may be adjusted, replaced, or stopped if necessary
  - infection screening: rubella, HBsAg, VDRL, Pap smear, gonorrhea/chlamydia, HIV, TB testing based on travel and working in health care, history of varicella or vaccination, parvovirus immunity if exposed to small children, cytomegalovirus immunity if health care worker, and toxoplasmosis serology in case of proximity to cats or gardening
  - genetic testing as appropriate for high risk groups (see *Prenatal Screening*, Table 2); consider genetics referral in known carriers, recurrent pregnancy loss/stillbirth, family members with developmental delay, birth anomalies, genetic diseases, and consanguinity

**Family doctors and midwives to consider OB consultation if:**
- Insulin-dependent GDM
- VBAC
- HTN
- Multiple gestation
- Malpresentation
- Active antepartum hemorrhage
- PTL/PPROM
- Failure to progress/descend
- Induction/augmentation if high risk
- Tears: 3rd or 4th degree
- Retained placenta

Note: Guidelines vary by institution and by provincial midwifery colleges

Advise all women capable of becoming pregnant to supplement their diet with 0.4 mg/d of folic acid (CTFPHC Grade II-2-A Evidence)

Prenatal and genetic screening are voluntary and require proper counselling and informed consent before proceeding HIV is done automatically in some provinces as opt-out testing; need to inform patient of this

# Initial Prenatal Visit

- usually within 8-12 wk of the 1st day of LMP or earlier if <20 or >35 yr old, bleeding, very nauseous, or other risk factors present

### History

- gestational age by dates from the 1st day of the LMP
  - Naegele's rule: 1st day of LMP + 1 year + 7 d – 3 mo
  - e.g. LMP = 1 Apr 2014, EDD = 8 Jan 2015 (modify if cycle >28 d by adding number of d >28)
  - EDD by LMP not reliable if irregular menstrual cycle, or if patient unsure of the LMP
- if LMP unreliable, get a dating U/S which could coincide with nuchal translucency at ~12 wk
- EDD by T1 U/S more reliable than LMP if difference is greater than 5 d from LMP due date
- history of present pregnancy (e.g. bleeding, N/V) and all previous pregnancies
- past medical, surgical, and gynecological history
- prescription and non-prescription medications
- family history: genetic diseases, birth defects, multiple gestation, and consanguinity
- social history: smoking, alcohol, drug use, and domestic violence (see Family Medicine)

In history of previous pregnancies, **ALWAYS** ask:
GTPAL
Year
Sex
Weight
Gestational age
Mode of delivery
Length of labour
Complications

### Physical Exam

- complete physical exam to obtain baseline patient information – BP and weight important for interpreting subsequent changes
- BMI for risk stratification (risk of DVT, GDM, and pre-eclampsia all increase with greater BMI)

Ask every woman about abuse – not just those whose situations raise suspicion of abuse AND ask as early as possible in pregnancy

### Investigations

- blood work
  - CBC, blood group and Rh status, antibody screen, and infection screening as per preconception counselling
- urine R&M, midstream urine C&S
  - screen for bacteriuria and proteinuria
- pelvic exam
  - Pap smear (only if required according to patient history and provincial screening guidelines), cervical or urine PCR for *N. gonorrhoeae* (GC) and *C. trachomatis*

**Estimated Date of Delivery (EDD) Determination**
- By LMP if menses regular, patient reliable historian
- By T1 U/S if irregular menses
- By embryo age and date of transfer if IVF

- T1 U/S up to 13+6/7 weeks GA is most accurate method of establishing GA
- Changes to the EDD must be documented and discussed with the patient
- Pregnancy without U/S confirming or revising the EDD prior to 22+0/7 GA is considered sub-optimally dated

# Nausea and Vomiting

### Epidemiology

- affects 50-90% of pregnant women
- often limited to T1 but may persist beyond this

### Management
- rule out other causes of N/V especially if refractory to initial therapy
- weigh frequently, assess level of hydration, and test urine for ketones
- non-pharmacological
  - frequent small meals (bland, dry, salty are better tolerated), encourage any safe appealing foods
  - electrolyte oral solutions (Pedialyte®, Gatorade®)
  - stop prenatal vitamins and if T1, substitute with folic acid or adult/children's vitamins that are low in iron
  - increase sleep/rest
  - ginger (maximum 1000 mg/d)
  - acupuncture, acupressure, and mindfulness-based cognitive therapy
- pharmacological
  - first line: pyridoxine (B6) monotherapy or doxylamine/pyridoxine (Diclectin) combination 4 tablets PO daily (1 q am, 1 q lunch and 2 qhs) up to maximum of 8 tablets/d
  - H1 receptor antagonists should be considered for acute or chronic episodes of N/V in pregnancy
  - metoclopramide and phenothiazines can be used as an adjunctive therapy for severe N/V in pregnancy
  - Ondansetron if severe N/V and other anti-emetics have failed
- severe/refractory
  - consider homecare with IV fluids and parenteral anti-emetics, hospitalization

## Hyperemesis Gravidarum

### Definition
- intractable N/V, usually presents in T1 then diminishes; occasionally persists throughout pregnancy
- affects ~1% of pregnancies

### Etiology
- multifactorial with hormonal, immunologic, and psychological components
- rapidly rising β-hCG ± estrogen levels may be implicated

### Investigations
- rule out systemic causes: GI, pyelonephritis, thyrotoxicosis
- rule out other obstetrical causes: multiple gestation, GTN, HELLP syndrome
- CBC, electrolytes, BUN, creatinine, LFTs, urinalysis
- U/S

### Management
- thiamine supplementation may be indicated
- non-pharmacological (see *Nausea and Vomiting*, OB4)
- pharmacological options
  - doxylamine/pyridoxine (for dosage, see *Nausea and Vomiting*, OB4)
  - dimenhydrinate can be safely used as an adjunct to Diclectin® (1 suppository bid or 25 mg PO qid)
  - other adjuncts: hydroxyzine, pyridoxine, phenothiazine, metoclopramide
  - also consider: ondansetron or methylprednisolone (avoid steroids in T1 due to increased risk of oral clefting)
  - if severe: admit to hospital, NPO initially then small frequent meals; correct hypovolemia, electrolyte disturbance, and ketosis; TPN (if very severe) to reverse catabolic state

### Complications
- maternal
  - dehydration, electrolyte, and acid-base disturbances
  - Mallory-Weiss tear
  - Wernicke's encephalopathy, if protracted course
  - death
- fetal: usually none, IUGR is 15x more common in women losing >5% of pre-pregnancy weight

## Subsequent Prenatal Visits

### Timing
- for uncomplicated pregnancies, SOGC recommends q4-6 wk until 30 wk, q2-3 wk from 30 wk, and q1-2 wk from 36 wk until delivery

### Assess at Every Visit
- estimated GA
- history: fetal movements, uterine bleeding, leaking, cramping, questions, concerns
- physical exam: BP, weight gain, SFH, Leopold's maneuvers (T3) for lie, position, and presentation of fetus
- investigations: urinalysis for proteinuria in high risk women; fetal heart rate starting at 10-12 wk using Doppler U/S



**Symphysis Fundal Height**

**Symphysis Fundal Height (SFH)**

| | |
|---|---|
| 12 wk | Uterine fundus at pubic symphysis |
| 20 wk | Fundus at umbilicus |
| 20-36 wk | SFH should be within 2 cm of GA |

**SFH< Dates**
- Date miscalculation
- IUGR
- Fetal demise
- Oligohydramnios
- Early engagement

**SFH> Dates**
- Date miscalculation
- Multiple gestation
- Polyhydramnios
- large for gestational age (familial, DM)
- Fibroids

### Leopold's Maneuvers
- performed after 30-32 wk gestation
- first maneuver: to determine which fetal part is lying furthest away from the pelvic inlet
- second maneuver: to determine the location of the fetal back
- third maneuver: to determine which fetal part is lying above the pelvic inlet
- fourth maneuver: to locate the fetal brow

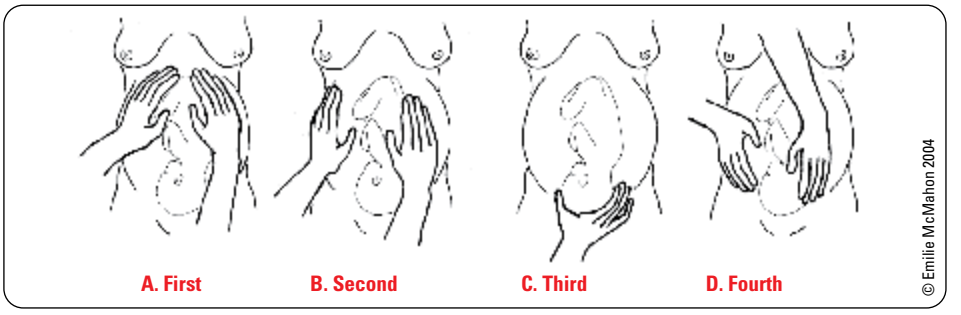



**Figure 2. Leopold's maneuvers (T3)**
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# Prenatal Screening and Diagnostic Tests

### Screening Tests
- testing should only occur following counselling and with informed consent from the patient

**Table 2. High-Risk Population Screening Tests**

| Disease (Inheritance) | Population(s) at Risk | Screening Test(s) |
|---|---|---|
| **Thalassemia (AR)** | Mediterranean, South East Asian, Western Pacific, African, Middle Eastern, Caribbean, South American | CBC (MCV and MCH), Hb electrophoresis, or HPLC |
| **Sickle Cell (AR)** | African, Caribbean, Mediterranean, Middle Eastern, Indian, South American | CBC (MCV and MCH), Hb electrophoresis, or HPLC |
| **Cystic Fibrosis (CF) (AR)** | Family history of CF in patient or partner or medical condition linked to CF like male infertility | CFTR gene DNA analysis |
| **Tay Sachs Disease (AR)** | Ashkenazi Jewish*, French Canadians, Cajun | Enzyme assay HEXA, or DNA analysis HEXA gene |
| **Fragile X Syndrome (X-linked)** | Family history – confirmed or suspected | DNA analysis: *FMR-1* gene |

AR = autosomal recessive; HEXA = hexosaminidase A; HPLC = high performance liquid chromatography
*If both partners are Ashkenazi Jewish, test for Canavan disease and Familial Dysautonomia (FD); if family history of a specific condition, look for carrier status: e.g. Gaucher, CF, Bloom syndrome, Niemann-Pick disease, etc. In all cases, if both partners are positive, refer for genetic counselling.

**Table 3. Gestation-Dependent Screening Investigations**

| Gestational Age (wk) | Investigations | Details |
|---|---|---|
| 8-12 | Dating U/S, possible Pap smear, chlamydia/gonorrhea testing, urine C&S (detect asymptomatic bacteriuria), HIV, VDRL, HepBsAg, Rubella IgG, Parvovirus IgM or IgG if high risk (small child at home or daycare worker/primary teacher), Varicella IgG if no history of disease/immunization, CBC, blood group and screen, urine C&S (detect asymptomatic bacteriuria) | |
| >10 | NIPT | Measures cell-free fetal DNA in maternal circulation |
| 10-12 | CVS | |
| 11-14 | Enhanced FTS<br>IPS Part 1 | Measures<br>1. Nuchal translucency on U/S<br>2. β-hCG<br>3. PAPP-A<br>4. Placental growth factor (enhanced FTS only)<br>5. MSAFP (enhanced FTS only) |
| 11-14 | Nuchal translucency U/S | |
| 15-16 to term | Amniocentesis | |
| 15-20 | IPS Part 2 | Measures<br>1. MSAFP<br>2. β-hCG<br>3. Unconjugated estrogen (estriol or μE3)<br>4. Inhibin A |



**Routine T2 U/S at 18-22 wk Helps Determine**
- Number of fetuses
- GA (if no prior U/S)
- Location of placenta
- Fetal anomalies

**Table 3. Gestation-Dependent Screening Investigations** (continued)

| Gestational Age (wk) | Investigations | Details |
|---|---|---|
| **15-20** | MSS | Measures<br>1. MSAFP<br>2. β-hCG<br>3. Unconjugated estrogen (estriol or μE3)<br>4. Inhibin A |
| **18-20 to term** | Fetal movements (quickening) | |
| **18-20** | U/S for dates, fetal growth, and anatomy assessment | |
| **24-28** | Gestational Diabetes Screen 50 g OGCT | See *Diabetes Mellitus*, OB26 |
| **28** | Repeat CBC<br>RhIG for all Rh-negative women | |
| **35-37** | GBS screen | See *Group B Streptococcus*, OB28 |
| **6 wk postpartum** | Discuss contraception, menses, breastfeeding, depression, mental health, support<br>Physical exam: breast exam, pelvic exam including Pap smear (only if due as per provincial screening) | |

Maternal serum screen is also referred to as Triple Screen; if Inhibin A is also tested, it is referred to as Quadruple Screen



**DDx of Increased MSAFP**
- Incorrect GA
- >1 fetus (e.g. twins)
- Fetal demise
- ONTD
- Abdominal wall defects (e.g. omphalocele)

## ULTRASOUND SCREENING
- 8-12 wk GA: dating U/S (most accurate form of pregnancy dating)
- measurement of crown-rump length (margin of error: ± 5 d)
- EDD should be based on T1 U/S if available
- 11-14 wk GA: NTUS
- measures the amount of fluid behind the neck of the fetus
- early screen for Trisomy 21 (may also detect cardiac and other aneuploidies like Turner syndrome)
- NT measurement is necessary for the FTS and IPS Part 1
- 18-20 wk GA: growth and anatomy U/S (margin of error: ± 10 d)
- earlier or subsequent U/S performed when medically indicated

## NON-INVASIVE PRENATAL TESTING (NIPT)
- analyses maternal blood for circulating cell-free fetal DNA (ccffDNA) at 9-10 wk GA onwards. Requires dating U/S for accuracy

### Advantages
- increased accuracy (high detection rate (DR), low false positive rate [FPR]) highly sensitive for Trisomy 21 (DR 99%, FPR 0.1- can also look for Trisomy 18 (DR 96%, FPR 0.1%), 13 (DR 91%, FPR 0.1%), Turner syndrome (DR 90%, FPR 0.2%), and some other disorders (DiGeorge syndrome, Cri Du Chat, Prader-Willi, Angelman syndrome, XY disorders)
- increased positive predictive value
- earlier timing with results available in 1-2 weeks where parents can potentially have a CVS at 11-13 weeks for diagnosis over an amniocentesis after 15 weeks

### Disadvantages
- does not screen for ONTD
- high cost to patient (only covered in some provinces [ON and BC] in certain cases)
- need to confirm with invasive testing (it is a screening test, not a diagnostic test)
- does not test for all aneuploidies
- gives no result in 1-5% of cases (insufficient fetal fraction more common with elevated BMI)
- not applicable to donor eggs

**Table 4. Comparison of FTS, MSS, and IPS**

| eFTS | MSS | IPS |
|---|---|---|
| 11-14 wk | 15-20 wk | 11-13 wk U/S-nuchal translucency<br>11-14 wk: eFTS blood<br>15-20 wk: MSS blood including inhibin A |
| Risk estimate for<br>1. Down syndrome (Trisomy 21): increased NT, increased β-hCG, decreased PAPP-A<br>2. Trisomy 18: increased NT, decreased PAPP-A, decreased β-hCG<br><br>Note: does not measure risk of ONTD and should be combined with MSAFP at 15-20 wk<br>Useful when patient wants results within the T1<br>More accurate estimate of Down syndrome risk than MSS, sensitivity ~85% (when combined with age)<br>5% false positive rate<br>Patients with positive screen should be offered CVS, amniocentesis, or NIPT (covered in some provinces, self-pay in others) | Risk estimate for<br>1. ONTD: increased MSAFP (sensitivity 80-90%)<br>2. Trisomy 21: decreased MSAFP, increased β-hCG, decreased μE3 (sensitivity 65%)<br>3. Trisomy 18: decreased MSAFP, decreased β-hCG, decreased μE3, decreased inhibin A (sensitivity 80%)<br>Only offered alone if patient missed the time window for IPS or eFTS<br>8% baseline false positive rate for Trisomy 21, lower for NTD and Trisomy 18<br>Patients with positive screen should be offered U/S, amniocentesis, or NIPT (covered in some provinces, self-pay in others) | Risk estimate for ONTD, Trisomy 21, Trisomy 18<br>Sensitivity ~85-90%<br>2% false positive rate<br>Patients with positive screen should be offered U/S and/or amniocentesis or NIPT (covered in some provinces, self-pay in others) |

Note: In twins, eFTS, MSS, and IPS are not applicable; screen with NT, NIPT for chromosomal abnormalities and MSAFP for ONTDs

### Diagnostic Tests
- Diagnostic tests available:
  - amniocentesis
  - chorionic villus sampling

### Indications
- age >35 yr (increased risk of chromosomal anomalies)
  - risk factors in current pregnancy
  - abnormal U/S
- abnormal prenatal screen (IPS, eFTS, or MSS)
- past history/family history of:
  - chromosomal anomaly or genetic disease
  - either parent a known carrier of a genetic disorder or balanced translocation
  - consanguinity
  - >3 spontaneous abortions

## AMNIOCENTESIS
- U/S-guided transabdominal extraction of amniotic fluid performed as early as 15 weeks GA

### Indications
- identification of genetic and chromosomal anomalies (15-16 wk gestation) as per indications above
- confirmation of positive NIPT testing
- positive eFTS/IPS/MSS
- assessment of fetal lung maturity (T3) via the L/S ratio (lecithin:sphingomyelin)
  - if >2:1, RDS is less likely to occur

### Advantages
- also screens for ONTD (acetylcholinesterase and amniotic AFP) – 96% accurate
- in women >35 yr, the risk of chromosomal anomaly (1/180) is greater than the risk of miscarriage from the procedure
- more accurate genetic testing than CVS

### Disadvantages
- 1/200 to 1/900 risk of procedure-related pregnancy loss, depending on local experience
- results take 14-28 d; QF-PCR or FISH can be done on chromosomes X, Y, 13, 18, 21, 22 to give preliminary results in 48 h



Compared to CVS, amniocentesis has a higher accuracy of prenatal cytogenetic diagnosis (99.8% vs. 97.5%) and lower risk of spontaneous abortion (0.5% vs. 1-2%)



**Risk Factors for Neural Tube Defects**

**GRIMM**
**G**enetics: family history of NTD (risk of having second child with NTD is increased to 2-5%), consanguinity, chromosomal (characteristic of Trisomy 13, 18, and 21)
**R**ace: European Caucasians > African Americans, 3-fold higher in Hispanics
**I**nsufficient vitamins: zinc and folate
**M**aternal chronic disease (e.g. DM)
**M**aternal use of antiepileptic drugs

General population risk for NTD is 0.1%

## CHORIONIC VILLUS SAMPLING
- biopsy of fetal-derived chorion using a transabdominal needle or transcervical catheter at 10-12 wk

### Advantages
- enables pregnancy to be terminated earlier than with amniocentesis
- rapid karyotyping and biochemical assay within 48 h, including FISH analysis
- high sensitivity and specificity

### Disadvantages
- 1% risk of procedure-related pregnancy loss
- does not screen for ONTD
- 1-2% incidence of genetic mosaicism "false negative" results

## ISOIMMUNIZATION SCREENING

### Definition
- isoimmunization: antibodies (Ab) produced against a specific RBC antigen (Ag) as a result of antigenic stimulation with RBC of another individual

### Etiology
- maternal-fetal circulation normally separated by placental barrier, but sensitization can occur and can affect the current pregnancy, or more commonly, future pregnancies
- anti-Rh Ab produced by a sensitized Rh-negative mother can lead to fetal hemolytic anemia
- risk of isoimmunization of an Rh-negative mother with an Rh-positive ABO-compatible infant is 16%
- sensitization routes
  - incompatible blood transfusions
  - previous fetal-maternal transplacental hemorrhage (e.g. ectopic pregnancy, abruption)
  - invasive procedures in pregnancy (e.g. prenatal diagnosis, cerclage, D&C)
  - any type of abortion
  - labour and delivery
  - trauma (e.g. car accident, fall, etc.)



**Rh Antibody Titre**
A positive titre (≥1:16) indicates an increased risk of fetal hemolytic anemia

### Investigations
- screening with indirect Coombs test at first visit for blood group, Rh status, and antibodies
- Kleihauer-Betke test used to determine extent of fetomaternal hemorrhage by estimating volume of fetal blood volume that entered maternal circulation
- detailed U/S for hydrops fetalis
- middle cerebral artery Dopplers are done to assess degree of fetal anemia; if not available, bilirubin is measured by serial amniocentesis to assess the severity of hemolysis
- cordocentesis for fetal Hb should be used cautiously (not first-line)



Standard dose of 300 µg of Rhogam® sufficient for 30 mL of fetal blood. Give additional 10 µg of Rhogam® for every mL of fetal blood over 30 mL

### Prophylaxis
- exogenous Rh IgG (Rhogam® or WinRho®) binds to Rh antigens of fetal cells and prevents them from contacting maternal immune system
- Rhogam® (120-300 µg) given to all Rh negative and antibody screen negative women in the following scenarios:
  - routinely at 28 wk GA (provides protection for ~12 wk)
  - within 72 h of the birth of a Rh positive fetus
  - with any invasive procedure in pregnancy (CVS, amniocentesis)
  - as part of management of ectopic pregnancy
  - with miscarriage or therapeutic abortion
  - with an antepartum hemorrhage
  - with trauma
- Rhogam® 300 µg provides sufficient prophylaxis for 30 mL fetal Rh positive whole blood
- a Kleihauer-Betke test or flow cytometry can be used to measure the relative quantity of fetal blood in maternal circulation to determine if additional Rhogam® is indicated (if >30 mL fetal blood)
- if Rh negative and Ab screen positive, follow mother with serial monthly Ab titres throughout pregnancy + U/S ± serial amniocentesis as needed (Rhogam® has no benefit, as B cells sensitized antibodies already in circulation)

### Treatment
- falling biliary pigment warrants no intervention (usually indicative of either unaffected or mildly affected fetus)
- intrauterine transfusion between 18-35 wk GA of O-negative packed RBCs may be required for severely affected fetus
- early delivery of the fetus for exchange transfusion following 35 wk GA

### Complications
- anti-Rh IgG can cross the placenta and cause fetal RBC hemolysis resulting in fetal anemia, CHF, edema, ascites
- severe cases can lead to hydrops fetalis (edema in at least two fetal compartments due to fetal heart failure secondary to anemia) or erythroblastosis fetalis (moderate to severe immune-mediated hemolytic anemia)

## Fetal Surveillance



**DDx of Decreased Fetal Movements**

**DASH**
**D**eath of fetus
**A**mniotic fluid decreased
**S**leep cycle of fetus
**H**unger/Thirst

- patients will generally first notice fetal movement ("quickening") at 18-20 wk in primigravidas; can occur 1-2 wk earlier in multigravidas; can occur 1-2 wk later if placenta is implanted on the anterior wall of uterus
- if the patient is concerned about decreased fetal movement, she is counselled to choose a time when the fetus is normally active to count movements (usually recommended after 26 wk)
- all high-risk women should be told to do FM counts
  - ≥6 movements in 2 h expected
  - If there is a subjective decrease in fetal movement, time how long it takes to feel 10 discreet movements, laying on the left in a quiet setting may facilitate feeling subtle movements
  - if 10 movements take more than 2 h, further assessment is indicated, and patient should present to labour and delivery triage for non-stress test

### NON-STRESS TEST



Normal NST: 2 accels, >15 bpm from baseline, lasting >15 s in 20 min

### Definition
- FHR tracing ≥20 min using an external Doppler to assess FHR and its relationship to fetal movement (see *Fetal Monitoring in Labour*, OB33)



**Describe NST**: baseline rate, absent/minimal/moderate/marked variability, accelerations present/not present, decelerations early/late/variable

### Indication
- any suggestion of uteroplacental insufficiency or suspected compromise in fetal well-being

**Table 5. Classification of Intrapartum EFM Tracings**

| | Normal Tracing (Category 1) | Atypical Tracing* (Category 2) | Abnormal Tracing* (Category 3) |
|---|---|---|---|
| **Baseline** | 110-160 bpm | 100-110 bpm or >160 bpm for <30 min<br>Rising baseline | Bradycardia <100 bpm<br>Tachycardia >160 for >30 min<br>Erratic baseline |
| **Variability** | 6-25 bpm (moderate)<br>≤5 (absent or minimal) for <40 min | 5 (absent or minimal) for 40-80 min | ≤5 for 80 min<br>Sinusoidal<br>25 bpm for >10 min |
| **Decelerations** | None or occasional variable <30 s | Variable decelerations<br>30-60 s duration | Variable decelerations >60 s<br>Late deceleration(s) |
| **Accelerations in Term Fetus** | 2 accelerations with acme of ≥15 bpm, lasting 15 s over <40 min of testing | 2 accelerations with acme of ≥15 bpm, lasting 15 s in 40-80 min | <2 accelerations with acme (peak) of contraction of ≥15 bpm, lasting 15 s in >80 min |
| **Accelerations in Preterm Fetus (<32 wk)** | >2 accelerations with acme of >10 bpm, lasting 10 s in <40 min | <2 accelerations with acme of >10 bpm, lasting 10 s in 40-80 min | <2 accelerations with acme of >10 bpm, lasting 10 s in >80 min |
| **Action** | FURTHER ASSESSMENT OPTIONAL, based on total clinical picture | FURTHER ASSESSMENT REQUIRED | URGENT ACTION REQUIRED An overall assessment of the situation and further investigation with U/S or BPP is required; some situations will require delivery |

Adapted from: SOGC, Fetal Health Surveillance: Antepartum and Intrapartum Consensus Guideline, September 2007



**Reassuring BPP (8/8)**

**LAMB**
**L**imb extension + flexion
**A**FV 2 cm x 2 cm
**M**ovement (3 discrete)
**B**reathing (one episode x 30 s)



Overlap >20 mm to the internal os in the T3 of pregnancy is highly predictive of the need for a C/S. Any degree of overlap after 35 wk is an indication for a C/S

### Operating Characteristics
- false positive rate depends on duration; false negative rate = 0.2-0.3%

### Interpretation
- normal: at least 2 accelerations of FHR >15 bpm from the baseline lasting >15 s in 20 min
- abnormal: <2 accelerations of FHR in 40 min
- if no observed accelerations or fetal movement in the first 20 min, stimulate fetus (fundal pressure, acoustic/vibratory stimulation) and continue monitoring for 30 min

## BIOPHYSICAL PROFILE

### Definition
- U/S assessment of the fetus ± NST

### Indications
- post-term pregnancy
- decreased fetal movement
- IUGR
- any other suggestion of fetal distress or uteroplacental insufficiency

**Table 6. Scoring of the BPP**

| Parameter | Reassuring (2 points) |
|---|---|
| **Tone** | At least one episode of limb extension followed by flexion |
| **Movement** | Three discrete movements |
| **Breathing** | At least one episode of breathing lasting at least 30 s |
| **Amniotic Fluid Volume (AFV)*** | Fluid pocket of 2 cm in 2 axes |

*AFV is a marker of chronic hypoxia, all other parameters indicate acute hypoxia

### Interpretation
- 8: perinatal mortality rate 1:1000; repeat BPP as clinically indicated
- 6: perinatal mortality 31:1000; repeat BPP in 24 h
- 0-4: perinatal mortality rate 200:1000; deliver fetus if benefits of delivery outweigh risks

# Counselling of the Pregnant Woman

## Nutrition

- Canada's Food Guide to Healthy Eating suggests
  - eating a varied diet with plenty of vegetables and fruits, whole grains, dairy products, and lean meats or plant proteins
  - caloric increase of ~100 kCal/d in the T1, ~300 kCal/d in the T2 and T3, and ~450 kCal/d during lactation (less if BMI >25)
  - daily multivitamin with folic acid should be continued during pregnancy

### Nutrients in Pregnancy

- folate: 0.4-1 mg/d for first 12 wk (5 mg/d if high risk)
  - supports increase in blood volume, growth of maternal and fetal tissue, and decrease in incidence of NTD
  - foods rich in folic acid include: spinach, lentils, chick peas, asparagus, broccoli, peas, brussels sprouts, corn, and oranges
- calcium: 1200-1500 mg/d
  - maintains integrity of maternal bones, skeletal development of fetus, and breast milk production
- vitamin D: 1000 IU
  - promotes calcium absorption
- iron: 0.8 mg/d in T1, 4-5 mg/d in T2, and >6 mg/d in T3
  - supports maternal increase in blood cell mass, supports fetal and placental tissue
  - required amounts exceed normal body stores and typical intake, and therefore need supplemental iron
  - iron is the only known nutrient for which requirements during pregnancy cannot be met by diet alone (see *Iron and Folate Deficiency Anemia*, OB26)
- essential fatty acids – supports fetal neural and visual development
  - contained in vegetable oils, margarines, peanuts, and fatty fish

### Caffeine

- diuretic and stimulant that readily crosses placenta
- less than 300 mg/d is considered safe
- relationship between caffeine and IUGR is unknown (ACOG)
- SOGC states 1-2 cups/d are safe during pregnancy



**Sources of Caffeine**
- 5 oz cup coffee: 40-180 mg
- 5 oz brewed tea: 20-90 mg
- 12 oz cola: 46 mg
- Red Bull®: 67 mg
- Dark chocolate bar: 10 mg
- 8 oz hot chocolate: 5 mg

### Herbal Teas and Preparations

- not enough scientific information about safety of various herbs and herbal products to recommend their use during pregnancy
- some herbal teas can have toxic or pharmacological effects on the mother or fetus
- raspberry leaf tea often used at term to promote labour
- herbal teas considered safe in moderation (2-3 cups/d): citrus peel, ginger, lemon balm, linden flower (unless cardiac condition), orange peel, and rose hip

### Foodborne Illnesses

- microbiological contamination of food may occur through cross-contamination and/or improper food handling
  - listeriosis (*Listeria monocytogenes*) and toxoplasmosis (*Toxoplasma gondii*) are of concern during pregnancy
  - avoid consumption of raw meats and fish, raw hotdogs, raw eggs, raw sprouts (especially alfalfa), and unpasteurized dairy products or juices
  - avoid unpasteurized soft cheeses, deli meats, smoked salmon, and pâtés as they may be sources of Listeria
- chemical contamination of food
  - current guideline for mercury of 0.5 ppm in fish is not considered harmful for the general population, including pregnant women
  - Health Canada advises pregnant women to limit consumption of top predator fish such as shark, swordfish, king mackerel, and tilefish

## Lifestyle

- exercise under physician guidance; "talk test" = should be able to speak while exercising; avoid supine position after 20 wk GA
- absolute contraindications
  - ruptured membranes, preterm labour, hypertensive disorders of pregnancy, incompetent cervix, IUGR, multiple gestations (>3), placenta previa after 28 wk, persistent T2 or T3 bleeding, uncontrolled type I DM, uncontrolled thyroid disease, serious cardiovascular or respiratory disease, and other systemic disorders

- relative contraindications
  - recurrent pregnancy loss, gestational hypertension, history of spontaneous preterm birth, mild/moderate cardiovascular or respiratory disease, symptomatic anemia, malnutrition, eating disorder, twin pregnancy after 28 wk, and other significant medical conditions
- weight gain: optimal gain depends on pre-pregnancy BMI (varies from 6.8-18.2 kg)
- work: strenuous work, extended hours and shift work during pregnancy may be associated with greater risk of low birth weight, prematurity, and spontaneous abortion
- air travel acceptable in T2; airline cut off for travel is 36-38 wk gestation depending on the airline, to avoid giving birth on the plane
- sexual intercourse: may continue, except in patients at risk for: abortion, preterm labour, or placenta previa; breast stimulation may induce uterine activity, and is discouraged in high-risk patients near term
- smoking: assist/encourage to reduce or quit smoking
  - increased risk of decreased birth weight, placenta previa/abruption, spontaneous abortion, preterm labour, and stillbirth
- alcohol: no amount of alcohol is safe in pregnancy; encourage abstinence from alcohol during pregnancy; alcohol increases incidence of abortion, stillbirth, and congenital anomalies
  - fetal alcohol syndrome (see Pediatrics, P24)
- cocaine: microcephaly, growth retardation, prematurity, and abruptio placentae
- marijuana: smoking associated with low birth weight infants
- biopsychosocial considerations: discuss birth plan, offer community maternal resources

**Weight Gain in Pregnancy**

| BMI | Total Gain | Weekly Gain in T2 & T3 |
|---|---|---|
| <18.5 | 28-40 lb | 1-1.3 lb/wk |
| 18.5-24.9 | 25-35 lb | 1 lb/wk |
| >25-29.9 | 15-25 lb | 0.5-0.7 lb/wk |
| >30 | 11-20 lb | 0.4-0.6 lb/wk |

# Medications

- most drugs cross the placenta to some extent
- very few drugs are teratogenic, but very few drugs have proven safety in pregnancy
- use any drug with caution and only if necessary
- analgesics: acetaminophen preferable to ASA or ibuprofen

**Table 7. Documented Adverse Effects, Weigh Benefits vs. Risks, and Consider Medication Change**

| Contraindicated Medication | Adverse Effect |
|---|---|
| **ACE Inhibitor** | Fetal renal defects, IUGR, oligohydramnios |
| **Carbamazepine** | ONTD in 1-2% |
| **Chloramphenicol** | Grey baby syndrome (fetal circulatory collapse 2° to toxic accumulation) |
| **Lithium** | Ebstein's cardiac anomaly, goitre, hyponatremia |
| **Misoprostol** | Mobius syndrome (congenital facial paralysis with or without limb defects), spontaneous abortion, preterm labour |
| **NSAIDs** | Premature closure of the ductus arteriosus after 30 wk GA (prior to that, indomethacin used for tocolysis) |
| **Phenytoin** | Fetal hydantoin syndrome in 5-10% (IUGR, mental retardation, facial dysmorphogenesis, congenital anomalies) |
| **Retinoids (e.g. Accutane®)** | CNS, craniofacial, cardiac, and thymic anomalies |
| **Sulpha drugs** | Anti-folate properties, therefore theoretical risk in T1; risk of kernicterus in T3 |
| **Tetracycline** | Stains infant's teeth, may affect long bone development |
| **Valproate** | Congenital malformation (including ONTD) up to 9% |
| **Warfarin** | Increased incidence of spontaneous abortion, stillbirth, prematurity, IUGR, fetal warfarin syndrome (nasal hypoplasia, epiphyseal stippling, optic atrophy, mental retardation, intracranial hemorrhage) |

**Drug Resources During Pregnancy and Breastfeeding**
- Hale T. Medications and mothers' milk, 11th ed. Pharmasoft Publishing, 2004
- Lactmed: https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm

# Immunizations

## Intrapartum
- administration is dependent on the risk of infection vs. risk of immunization complications
- safe: tetanus toxoid, diphtheria, influenza, hepatitis B, and pertussis
- avoid live vaccines (risk of placental and fetal infection): polio, measles/mumps/rubella, and varicella
- contraindicated: oral typhoid
- the Public Health Agency of Canada recommends:
  - all pregnant women receive the influenza vaccine
  - all pregnant women should be given Tdap every pregnancy irrespective of immunization history ideally between 27-32 weeks but can be given at 13-26 weeks if high risk of preterm labour. If Tdap was given in T1 (i.e. prior to pregnancy recognition), it does not need to be repeated

## Postpartum
- rubella vaccine for all non-immune mothers. If they have had an adult booster and remain non-immune, they should not be revaccinated and pregnancy should be deferred for at least 1 mo following vaccination
- hepatitis B vaccine should be given to infant within 12 h of birth if maternal status unknown or positive – follow-up doses at 1 and 6 mo
- any vaccine required/recommended is generally safe postpartum

# Radiation

- ionizing radiation exposure is considered teratogenic at high doses
  - if indicated for maternal health, should be done
- imaging not involving direct abdominal/pelvic high dosage radiation is not associated with adverse effects
  - higher dosage to fetus: plain x-ray of lumbar spine/abdomen/pelvis, barium enema, CT abdomen/pelvis/lumbar spine
- radioactive isotopes of iodine are contraindicated
- no known adverse effects from U/S or MRI (long-term effects of gadolinium unknown, avoid if possible)

**Table 8. Approximate Fetal Doses from Common Diagnostic Procedures**

| Examination | Estimated Fetal Dose (cGy) | Number of Exams Safe in Pregnancy |
|---|---|---|
| **Plain Film** | | |
| Abdomen | 0-14 | 35 |
| Pelvis | 0-11 | 45 |
| Lumbar spine | 0-17 | 29 |
| Thoracic spine | 0.009 | 555 |
| Chest (2 views) | <0.001 | 5000 |
| **CT** | 0-8 | 6 |
| Abdomen | 2-5 | 2 |
| Pelvis | 0-24 | 20 |
| Lumbar spine | 0.006 | 833 |
| Chest | | |

Adapted from: Cohen-Kerem, et al. 2005 and Valentin 2000



**Radiation in Pregnancy**
- Necessary amount to cause miscarriage: >5 cGy
- Necessary amount to cause malformations: >20-30 cGy

# Obstetrical Hemorrhage



## Definition
- vaginal bleeding from 20 wk to term

## Differential Diagnosis
- bloody show (represents cervical changes/early stages of dilation) – most common etiology in T3
- placenta previa
- abruptio placentae – most common pathological etiology in T3
- vasa previa
- cervical lesion (cervicitis, polyp, ectropion, cervical cancer)
- uterine rupture
- other: bleeding from bowel or bladder, abnormal coagulation

**Table 9. Comparison of Placenta Previa and Abruptio Placentae**

| | Placenta Previa | Abruptio Placentae |
|---|---|---|
| **Definition** | Abnormal location of the placenta near, partially, or completely over the internal cervical os | Premature separation of a normally implanted placenta after 20 wk GA |
| **Etiology** | Idiopathic | Idiopathic |
| **Epidemiology** | 0.5-0.8% of all pregnancies | 1-2% of all pregnancies |
| **Risk Factors** | History of placenta previa (4-8% recurrence risk)<br>Multiparity<br>Increased maternal age<br>Multiple gestation<br>Uterine tumour (e.g. fibroids) or other uterine anomalies<br>Uterine scar due to previous abortion, C/S, D&C, myomectomy | Previous abruption (recurrence rate 5-16%)<br>Maternal HTN (chronic or gestational HTN in 50% of abruptions) or vascular disease<br>Cigarette smoking (>1 pack/d), excessive alcohol consumption, cocaine<br>Multiparity and/or maternal age >35 yr<br>PPROM<br>Rapid decompression of a distended uterus (polyhydramnios, multiple gestation)<br>Uterine anomaly, fibroids<br>Trauma (e.g. motor vehicle collision, maternal battery) |
| **Bleeding** | PAINLESS | Usually PAINFUL |

# Placenta Previa



## Definition
- placenta implanted in the lower segment of the uterus, presenting ahead of the leading pole of the fetus
- placental position is described in relation to the internal os as "mm away" or "mm of overlap"

## Clinical Features
- PAINLESS bright red vaginal bleeding (recurrent), may be minimized and cease spontaneously but can become catastrophic
- mean onset of bleeding is 30 wk GA, but onset depends on degree of previa
- physical exam
  - do not perform digital vaginal exam until ruling out placenta previa
  - uterus soft and non-tender
  - presenting fetal part high or displaced
  - FHR usually normal
  - shock/anemia correspond to degree of apparent blood loss
- complications
  - fetal
    - perinatal mortality low but still higher than with a normal pregnancy
    - prematurity (bleeding often dictates early C/S)
    - intrauterine hypoxia (acute or IUGR)
    - fetal malpresentation
    - PPROM
    - risk of fetal blood loss from placenta, especially if incised during C/S
  - maternal
    - <1% maternal mortality
    - hemorrhage and hypovolemic shock, anemia, acute renal failure, and pituitary necrosis (Sheehan syndrome)
    - placenta accreta – especially if previous uterine surgery or anterior placenta previa
    - hysterectomy

## Investigations
- transvaginal U/S is more accurate than transabdominal U/S at diagnosing placenta previa at any gestational age
- spontaneously resolution is likely with increasing uterine distention if the placenta obscures the internal os by less than 20 mm at 20 wk GA
- transvaginal U/S should be repeated in the T3 as continued change in the placental location is likely



Do NOT perform a vaginal exam until placenta previa has been ruled out by U/S

## Management
- goal: keep pregnancy intrauterine until the risk of continuing pregnancy outweighs the risk of preterm delivery
- stabilize and monitor
  - maternal stabilization: large bore IV with hydration, $O_2$ for hypotensive patients
  - maternal monitoring: vitals, urine output, blood loss, blood work (hematocrit, CBC, INR/PTT, platelets, fibrinogen, FDP, type and cross match)
  - electronic fetal monitoring
  - U/S assessment: when fetal and maternal conditions permit, determine fetal viability, GA, and placental position
- Rhogam® if mother is Rhnegative
- Kleihauer-Betke test to determine extent of fetomaternal transfusion and administer Rhogam® at adequate dose
- GA <37 wk and minimal bleeding: expectant management
  - admit to hospital
  - limited physical activity, no douches, enemas, or sexual intercourse
  - consider corticosteroids for fetal lung maturity
  - delivery when fetus is mature or hemorrhage indicating maternal or fetal compromise
- GA ≥37 wk – deliver by C/S

# Abruptio Placentae

## Definition
- partial or total placental detachment that is premature and caused by bleeding at the decidual-placental interface
- occurring >20 wk gestation

## Clinical Features
- classification
  - total (fetal death inevitable) vs. partial
  - external/revealed/apparent: blood dissects downward toward cervix
  - internal/concealed/occult (20%): blood dissects upward toward fetus, may or may not present with vaginal bleeding
  - most are mixed
- presentation
  - usually PAINFUL (80%) vaginal bleeding (bleeding not always present if abruption is concealed), uterine tenderness, uterine contractions/hypertonus
  - pain: sudden onset, constant, localized to lower back and uterus
  - shock/anemia out of proportion to apparent blood loss
  - ± fetal distress, fetal demise (15% present with demise), bloody amniotic fluid (fetal presentation typically normal)
  - ± coagulopathy

Abruptio placentae is the most common cause of DIC in pregnancy

## Complications
- fetal complications: perinatal mortality 25-60%, prematurity, intrauterine hypoxia
- maternal complications: <1% maternal mortality, DIC (in 20% of abruptions), acute renal failure, anemia, hemorrhagic shock, pituitary necrosis (Sheehan syndrome), or amniotic fluid embolus

## Investigations
- clinical diagnosis, U/S not sensitive for diagnosing abruption (sensitivity = 15%)

## Management
- maternal stabilization: large bore IV with hydration, $O_2$ for hypotensive patients
- maternal monitoring: vitals, urine output, blood loss, blood work (hematocrit, CBC, PTT/PT, platelets, fibrinogen, FDP, type and cross match)
- electronic fetal monitoring
- blood products on hand (red cells, platelets, cryoprecipitate) because of DIC risk
- Rhogam® if Rh negative
  - Kleihauer-Betke test may confirm abruption
- abruption without fetal/maternal compromise (mild abruption)
  - GA <37 wk: use serial Hct to assess concealed bleeding, deliver when fetus is mature or when hemorrhage dictates
  - GA ≥37 wk: stabilize and deliver
- abruption with fetal/maternal compromise (moderate to severe abruption)
  - hydrate and restore blood loss and correct coagulation defect if present
  - vaginal delivery if no contraindication and no evidence of fetal or maternal distress
  - C/S if live fetus and fetal or maternal distress develops with fluid/blood replacement, labour fails to progress, or if vaginal delivery otherwise contraindicated

**Kleihauer-Betke Test**
Quantifies fetal cells in the maternal circulation

# Vasa Previa

## Definition
- unprotected fetal vessels pass over the cervical os; associated with velamentous insertion of cord into membranes of placenta or succenturiate (accessory) lobe

## Epidemiology
- 1 in 5000 deliveries – higher in twin pregnancies

## Clinical Features
- PAINLESS vaginal bleeding and fetal distress (tachy-to-bradyarrhythmia in a sinusoidal pattern)
- if undiagnosed, 50% perinatal mortality, increasing to 75% if membranes rupture (most infants die of exsanguination)
- if diagnosed antenatally on U/S without labour or symptoms, then 97% survival

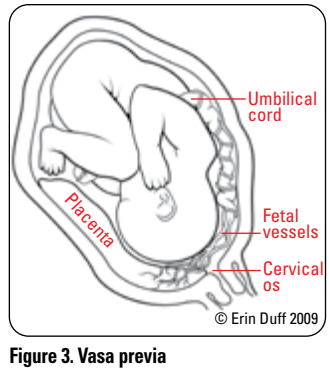


**Figure 3. Vasa previa**

## Investigations
- Apt test (NaOH mixed with the blood) can be done immediately to determine if the source of bleeding is fetal (supernatant turns pink) or maternal (supernatant turns yellow)
- Wright's stain on blood smear and look for nucleated red blood cells (in cord, not maternal blood)

## Management
- planned C/S (35-36 weeks) or if bleeding, emergency C/S (since bleeding is from fetus, a small amount of blood loss can have catastrophic consequences)

# Obstetrical Complications

## Preterm Labour

### Definition
- labour between 20 and 37 wk gestation

### Etiology
- idiopathic (most common)
- maternal: infection (recurrent pyelonephritis, untreated bacteriuria, chorioamnionitis), HTN, DM, chronic illness, mechanical factors (previous obstetric, gynecological, and abdominal surgeries); socio-environmental (poor nutrition, smoking, drugs, alcohol, stress), pre-eclampsia
- maternal-fetal: PPROM (common), polyhydramnios, placenta previa, abruptio placentae, or placental insufficiency
- fetal: multiple gestation, congenital abnormalities, fetal hydrops
- uterine: excessive enlargement (hydramnios, multiple gestation), malformations (intracavitary leiomyomas, septate uterus, and Müllerian duct abnormalities)

### Epidemiology
- preterm labour complicates about 10% of pregnancies

### Risk Factors
- prior history of spontaneous PTL is the most important risk factor
- prior history of large or multiple cervical excisions (cone biopsy) or mechanical dilatation (D&C)
- cervical length: measured by transvaginal U/S (cervical length >30 mm has high negative predictive value for PTL before 34 wk)
- identification of bacterial vaginosis and ureaplasma urealyticum infections
  - routine screening not supported by current data, but it is reasonable to screen high-risk women
- family history of preterm birth
- smoking
- late maternal age
- multiple gestation

### Prevention of Preterm Labour
**A. Cervical Cerclage**
- **definition**: placement of cervical sutures at the level of the internal os, usually at the end of the T1 or in the T2 and removed in the T3
- indications: cervical incompetence (i.e. cervical dilation and effacement in the absence of increased uterine contractility)
- diagnosis of cervical incompetence
  - obstetrical Hx: silent cervical dilation, recurrent T2 losses, cervical procedures such as loop excisions
  - ability of cervix to hold an inflated Foley catheter during a hysterosonogram
  - transvaginal U/S of cervical length is recommended only for high-risk pregnancies and only before 30 wk GA
- proven benefit in the prevention of PTL in women with primary structural abnormality of the cervix (e.g. conization of the cervix, connective tissue disorders)

**B. Progesterone**
- progesterone thought to maintain uterine quiescence; however exact mechanism of action is unclear
- if previous PTL: 17-alphahydroxyprogesterone 250 mg IM weekly from 16+0 to 36 wk GA
- if short cervix: 200 mg daily vaginally from time of diagnosis to 36 wk GA
- superior to cerclage in preventing preterm labour of singletons not due to cervical incompetence

**C. Lifestyle Modification**
- smoking cessation, substance use reduction, treatment of GU infections (including asymptomatic UTIs), and patient education regarding risk factors

### Predicting PTL
- fetal fibronectin: a glycoprotein in amniotic fluid and placental tissue
  - positive if >50 ng/mL; NPV > PPV
  - done if 1 or more signs of preterm labour (regular contractions >6/h, pelvic pressure, low abdominal pain and/or cramps, low backache)
  - done only if: 24-34 weeks, intact membranes, <3 cm dilated, established fetal well being
  - contraindicated as well if: cerclage, active vaginal bleeding, vaginal exam, or sex in last 24 h
  - if negative, not likely to deliver in 7-14 d (>95% accuracy); if positive increased risk of delivery, may need admission/transfer to centre that can do delivery ± tocolysis and/or corticosteroids

### Clinical Features
- regular contractions (2 in 10 min, >6/h)
- cervix >1 cm dilated, >80% effaced, or length <2.5 cm



Preterm labour is the most common cause of neonatal mortality in the US



Positive fetal fibronectin in cervicovaginal fluid (>50 ng/mL) at 24 wk gestation predicted spontaneous PTL at <34 wk with sensitivity of 23%, specificity of 97%, PPV of 25%, NPV of 96%



**Ultrasonographic Cervical Length Assessment in Predicting Preterm Birth in Singleton Pregnancies**
J Obstet Gynaecol Can 2018;40(2);154-61
**Recommendations:**
1. Transabdominal ultrasonography should not be used for cervical length assessment to predict preterm birth (II-2D).
2. Transvaginal ultrasonography is the preferred route for cervical assessment to identify women at increased risk of spontaneous preterm birth and may be offered to women at increased risk of preterm birth (II-2B).
3. Transperineal ultrasonography may be offered to women at increased risk of preterm birth if transvaginal ultrasonography is either unacceptable or unavailable (II-2B).
4. Because of poor positive predictive values and sensitivities and lack of proven effective interventions, routine transvaginal cervical length assessment is not recommended in women at low risk (II-2E).
5. In women presenting with suspected preterm labour, transvaginal sonographic assessment of cervical length may be used to help in determining who is at high risk of preterm delivery and may be helpful in preventing unnecessary intervention. It is unclear whether this information results in a reduced risk of preterm birth (II-2B).
6. In asymptomatic women with a history of spontaneous preterm birth and an ultrasonographically diagnosed short cervical length (<25 mm) prior to 24 weeks of gestation, cervical cerclage should be considered to reduce the risk of preterm birth (I-B).
7. In all asymptomatic women who present with membranes at or protruding past the external cervical os, an emergency cerclage should be considered to reduce the risk of preterm delivery (I-B).

## Management

**A. Initial**

- transfer to appropriate facility if stable
  - tocolysis and first dose of antenatal steroids prior to transfer
- hydration (normal saline at 150 mL/h)
- bed rest in left lateral decubitus position to reduce aortocaval compression and improve cardiac output
- sedation (morphine)
- avoid repeated pelvic exams (increased infection risk)
- U/S examination of fetus (GA, BPP, position, placenta location, estimated fetal weight)
- prophylactic antibiotics; (for GBS) important to consider if PPROM (e.g. erythromycin controversial, but may help to delay delivery)

**B. Tocolysis (Suppression of Labour)**

- does not inhibit preterm labour completely, but may delay delivery (used for <48 h) to allow for betamethasone valerate (Celestone®) and/or transfer to appropriate centre for care of the premature infant
- requirements (all must be satisfied)
  - preterm labour
  - live, immature fetus, intact membranes, cervical dilatation of <4 cm
  - absence of maternal or fetal contraindications
- contraindications
  - maternal: bleeding (placenta previa or abruption), maternal disease (HTN, DM, heart disease), preeclampsia or eclampsia, chorioamnionitis
  - fetal: erythroblastosis fetalis, severe congenital anomalies, fetal distress/demise, IUGR, multiple gestation (relative)
- agents
  - calcium channel blockers: nifedipine
    - 20 mg PO loading dose followed by 20 mg PO 90 min later
    - 20 mg can be continued q3-8h for 72 h or to a max of 180 mg
    - 10 mg PO q20min x 4 doses
    - relative contraindications: nifedipine allergy, hypotension, hepatic dysfunction, concurrent beta-mimetics or magnesium sulfate use, transdermal nitrates, or other antihypertensive medications
    - absolute contraindications: maternal congestive heart failure, aortic stenosis
  - prostaglandin synthesis inhibitors: indomethacin
    - 1st line for early preterm labour (<30 wk GA) or polyhydramnios
    - 50-100 mg PR loading dose followed by 25-50 mg q6h x 8 doses for 48 hours

**C. Antenatal Corticosteroids**

- betamethasone valerate (Celestone®) 12 mg IM q24h x 2 doses or dexamethasone 6 mg IM q12h x 4 doses
  - given between 24 to 33+6 wk GA if expected to deliver in the next 7 d
  - women between 22+0 and 23+6 wk GA at high risk of preterm birth within the next 7 d should be provided with multidisciplinary consultation regarding high likelihood for severe perinatal morbidity and mortality and associated maternal morbidity – consider antenatal corticosteroids therapy if early intensive care is requested and planned
  - specific maternal contraindications: active TB
- enhance fetal lung maturity, reduce perinatal death, reduce incidence of severe RDS, and intraventricular hemorrhage, necrotizing enterocolitis, and neonatal sepsis

**D. Neuroprotection**

- $MgSO_4$ 4 g bolus followed by 1 g/h infusion for at least 4 h if imminent delivery expected and <32 wk GA

## Prognosis

- prematurity is the leading cause of perinatal morbidity and mortality
- 24 wk = 50% survival (may be higher in tertiary care centres with level 3-4 NICU)
- 30 wk or 1500 g (3.3 lb) = 90% survival
- 33 wk or 2000 g (4.4 lb) = 99% survival
- morbidity due to asphyxia, hypoxia, sepsis, RDS, intraventricular cerebral hemorrhage, thermal instability, retinopathy of prematurity, bronchopulmonary dysplasia, necrotizing enterocolitis

**Cerclage for Short Cervix on Ultrasonography in Women with Singleton Gestations and Previous Preterm Birth**
Obstet Gynecol 2011;117:663-71
**Purpose**: To determine if cerclage prevents preterm birth (<35 wk gestation) and perinatal mortality and morbidity among women with previous spontaneous preterm birth, asymptomatic singleton gestation, and short cervical length (<25 mm before 24 wk gestation) on transvaginal ultrasonography.
**Methods**: Meta-analysis of randomized trials identified using searches on MEDLINE, PUBMED, EMBASE, and the Cochrane Library.
**Results**: 5 trials included. Preterm birth was significantly lower among women receiving cerclage vs. those not receiving (RR = 0.70, 95% CI 0.55-0.89). Cerclage also significantly reduced preterm birth before 24, 28, 32, and 37 wk gestation. Perinatal mortality and morbidity were significantly lower in the cerclage group (RR = 0.64, 95% CI 0.45-0.91).
**Conclusions**: Cerclage significantly prevents preterm birth and perinatal mortality and morbidity in this specific group of women.

**Tocolytics for Preterm Premature Rupture of Membranes**
Cochrane DB Syst Rev 2014;2:CD007062
**Purpose**: To assess the potential benefits and harms of tocolysis in women with PPROM.
**Selection Criteria**: Pregnant women with singleton pregnancies and PPROM (23-36 wk and 6 d GA).
**Results**: 8 studies with 408 women total. Prophylactic tocolysis with PPROM was associated with increased overall latency, without additional benefits for maternal/neonatal outcomes. For women with PPROM before 34 wk, there was a significantly increased risk of chorioamnionitis in women who received tocolysis. Neonatal outcomes were not significantly different.
**Conclusion**: Although there are limitations to the studies, there is currently insufficient evidence to support tocolytic therapy for women with PPROM, as there was an increase in maternal chorioamnionitis without significant benefits to the infant.

# Premature Rupture of Membranes

## Definitions

- PROM: premature (pre-labour) rupture of membranes at any GA
- prolonged ROM: >24 h elapsed between rupture of membranes and onset of labour
- preterm ROM: ROM occurring before 37 wk gestation
- PPROM: preterm (before 37 wk) AND premature (pre-labour) rupture of membranes

**Membrane status determined by**

- Pooling of fluid on speculum exam
- Increased pH of vaginal fluid (nitrazine test)
- Ferning of fluid under light microscopy
- Decreased AFV on U/S

## Risk Factors

- maternal: multiparity, cervical incompetence, infection (cervicitis, vaginitis, STI, UTI), family history of PROM, low socioeconomic class/poor nutrition
- fetal: congenital anomaly, multiple gestation
- other risk factors associated with PTL

## Clinical Features

- history of fluid gush or continued leakage

### Investigations
- sterile speculum exam (avoid introduction of infection)
  - pooling of fluid in the posterior fornix
  - cascading: fluid leaking out of cervix with cough/valsalva
- nitrazine (basic amniotic fluid turns nitrazine paper blue)
  - low specificity as it can also be positive with blood, urine, or semen
- ferning: salt in amniotic fluid evaporates, giving amniotic fluid the appearance of ferns on microscopy
- U/S to rule out fetal anomalies; assess GA, presentation, and BPP

### Management
- admit for expectant management and monitor vitals q4h, daily NST, WBC count, increased surveillance
- avoid introducing infection by minimizing examinations
  - consider administration of betamethasone valerate (Celestone®) to accelerate maturity if <34 weeks if no evidence of infection
  - consider tocolysis for 48 h to permit administration of steroids if PPROM induces labour
- screen women for UTIs, STIs, GBS infection and treat with appropriate antibiotics if positive (treat GBS at time of labour)
- if not in labour or labour not indicated, consider antibiotics: penicillins or macrolide antibiotics are the antibiotics of choice
- deliver urgently if evidence of fetal distress and/or chorioamnionitis

**Table 10. PROM Management**

| Degree of Prematurity | Management |
|---|---|
| 22-25 wk | Individual consideration with counselling of parents regarding risks to preterm infants |
| 26-34 wk | Expectant management as prematurity complications are significant |
| 34-36 wk | "Grey zone" where risk of death from RDS and neonatal sepsis is the same |
| ≥37 wk | Induction of labour since the risk of death from sepsis is greater than RDS |

### Prognosis
- varies with gestational age
- 90% of women with PROM at 28-34 wk GA go into spontaneous labour within 1 wk
- 50% of women with PROM at <26 wk GA go into spontaneous labour within 1 wk
- complications: cord prolapse, intrauterine infection (chorioamnionitis), premature delivery, limb contracture, and pulmonary hypoplasia especially at very early gestation

**Antibiotic Therapy in Preterm Premature Rupture of the Membranes**
J Obstet Gynaecol Can 2017;39(9):207-12
**Recommendations:**
1. Following PPROM at 32 weeks' gestation, antibiotics should be administered to women who are not in labour in order to prolong pregnancy and to decrease maternal and neonatal morbidity.
2. The benefit of antibiotics is greater at earlier gestational ages.
3. Antibiotics of choice are penicillins or macrolide antibiotics (erythromycin) in parenteral and/or oral forms. In patients allergic to penicillin, macrolide antibiotics should be used alone.
4. Two possible regimen options from large PPROM RCTs are: (1) ampicillin 2g IV q6h and erythromycin 250 mg IV q6h for 48 hours followed by amoxicillin 250 mg orally q8h and erythromycin 333 mg orally q8h for 5 d; (2) erythromycin 250 mg orally q6h for 10 d.
5. Amoxicillin/clavulanic acid should not be used because of an increased risk of necrotizing enterocolitis in neonates. Amoxicillin without clavulanic acid is safe.
6. Women presenting with PPROM should be screened for urinary tract infections, sexually transmitted infections, and group *B streptococcus*.

# Postterm Pregnancy

### Definition
- pregnancy >42 wk GA

### Epidemiology
- 41 wk GA: up to 27%
- >42 wk GA: 5.5%

### Etiology
- most cases idiopathic
- anencephalic fetus with no pituitary gland
- placental sulfatase deficiency (X-linked recessive condition in 1/2000-1/6000 infants) – rare

### Management (for singleton, cephalic fetus, otherwise uncomplicated)
- GA 39 wk with advanced maternal age (>40 y): consideration should be given to IOL due to increased risk of stillbirth
- GA 40-41 wk: expectant management
  - no evidence to support IOL or C/S unless other risk factors for morbidity are present (see prognosis)
- GA >41 wk: offer IOL if vaginal delivery is not contraindicated
  - IOL shown to decrease C/S, fetal heart rate changes, meconium staining, macrosomia, and death when compared with expectant management
- GA >41 wk and expectant management elected: serial fetal surveillance
  - fetal movement count by the mother
  - BPP q3-4d
- if AFI is decreased, labour should be induced

### Prognosis
- if >42 wk, perinatal mortality 2-3x higher (due to progressive uteroplacental insufficiency)
- with increasing GA, higher rates of: intrauterine infection, asphyxia, meconium aspiration syndrome, placental insufficiency, placental aging and infarction, macrosomia, dystocia, fetal distress, operative deliveries, pneumonia, seizures, requirement of NICU admission, stillbirth
- morbidity increased with HTN in pregnancy, DM, abruption, IUGR, and multiple gestation

# Intrauterine Fetal Demise

### Definition
- fetal demise in utero after 20 wk GA (before 20 wk GA called spontaneous abortion)

### Epidemiology
- occurring in 1% of pregnancies

### Etiology
- 50% idiopathic
- 50% secondary to HTN, DM, erythroblastosis fetalis, congenital anomalies, umbilical cord or placental complications, intrauterine infection, and APS

### Clinical Features
- decreased perception of fetal movement by mother
- SFH and maternal weight not increasing
- absent fetal heart tones on Doppler (not diagnostic)
- high MSAFP
- on U/S: no fetal heart rate. Depending on timing of death, may see skull collapse, brain tissue retraction, empty fetal bladder, non-filled aorta, or poor visualization of midline flax

### Management
- diagnosis: absent cardiac activity and fetal movement on U/S (required)
- determine secondary cause
  - maternal: HbA1c, fasting glucose, TSH, Kleihauer-Betke, VDRL, ANA, CBC, anticardiolipins, antibody screens, INR/PTT, serum/urine toxicology screens, cervical and vaginal cultures, and TORCH screen
  - fetal: karyotype, cord blood, skin biopsy, genetics evaluation, autopsy, amniotic fluid culture for CMV, parvovirus B19, and herpes
  - placenta: pathology, bacterial cultures

### Treatment
- <12 wk: dilation and curettage
- 13-20 wk: dilation and evacuation or sometimes IOL
- >20 wk: IOL
- monitor for maternal coagulopathy (10% risk of DIC)
- parental psychological care/bereavement support as per hospital protocol
- comprehensive discussion within 3 mo about final investigation and post-mortem results, help make plans for future pregnancies

**DIC: Generalized Coagulation and Fibrinolysis Leading to Depletion of Coagulation Factors**

**Obstetrical Causes**
- Abruption
- Gestational HTN
- Fetal demise
- PPH

**DIC-specific Blood Work**
- Platelets
- aPTT and PT
- FDP
- Fibrinogen

**Treatment**
- Treat underlying cause
- Supportive
- Fluids
- Blood products
- FFP, platelets, cryoprecipitate
- Consider anti-coagulation as VTE prophylaxis

# Intrauterine Growth Restriction

### Definition
- estimated fetal weight <10th percentile for GA on U/S, has not reached biologically determined growth potential

### Etiology/Risk Factors
- 50% unknown
- maternal causes
  - malnutrition, smoking, drug abuse, alcoholism, cyanotic heart disease, type 1 DM, SLE, pulmonary insufficiency, previous IUGR (25% risk, most important risk factor), and chronic HTN
- maternal
  - gestational HTN, chronic renal insufficiency, prolonged gestation, substance abuse, and poor nutrition
- placental
  - any disease that causes placental insufficiency
  - gross placental morphological abnormalities (infarction, hemangiomas, placenta previa, ansd abnormal cord insertion)
- fetal causes
  - TORCH infections, multiple gestation, and congenital anomalies/chromosomal abnormalities (10%)

### Clinical Features
- symmetric/type I (25-30%): occurs early in pregnancy
  - reduced growth of both head and abdomen
  - head:abdomen ratio may be normal (>1 up to 32 wk; =1 at 32-34 wk; <1 after 34 wk GA)
  - usually associated with congenital anomalies or TORCH infections
- asymmetric/type II (70%): occurs late in pregnancy
  - fetal abdomen is disproportionately smaller than fetal head
  - brain is spared; therefore head:abdomen ratio increased
  - usually associated with placental insufficiency
  - more favourable prognosis than type I

**TORCH**
**T**oxoplasmosis
**O**thers: e.g. syphilis
**R**ubella
**C**MV
**H**SV
• See Table 15, OB29

- complications
  - prone to meconium aspiration, asphyxia, polycythemia, hypoglycemia, hypocalcemia, hypophosphatemia, hyponatremia, and mental retardation
  - greater risk of perinatal morbidity and mortality

### Investigations
- SFH measurements at every antepartum visit (ensure accurate GA)
- if mother at high risk or SFH lags >2 cm behind GA
  - U/S for biparietal diameter, head and abdominal circumference ratio, femur length, fetal weight, AFV (decrease associated with IUGR), and decrease in the rate of growth
  - ± BPP
  - Doppler analysis of umbilical cord blood flow

### Management
- prevention via risk modification prior to pregnancy is ideal
- modify controllable factors: smoking, alcohol, nutrition, and treat maternal illness
- serial BPP (monitor fetal growth) and determine cause of IUGR, if possible
- delivery when extrauterine existence is less dangerous than continued intrauterine existence (abnormal function tests, absent growth, severe oligohydramnios) especially if GA >34 wk
- as IUGR fetuses are less likely to withstand stresses of labour, they are more likely to be delivered by Cesarean section

## Macrosomia

### Definition
- infant weight ≥90th percentile for a particular GA or >4000 g

### Etiology/Risk Factors
- maternal obesity, GDM, past history of macrosomic infant, prolonged gestation, multiparity

### Clinical Features
- increased risk of perinatal mortality
- CPD and birth injuries (shoulder dystocia, fetal bone fracture) more common
- complications of DM in labour (see Table 14, OB28)

### Investigations
- serial SFH
- further investigations if mother at high risk or SFH >2 cm ahead of GA
- U/S predictors
  - polyhydramnios
  - T3 abdominal circumference >1.5 cm/wk
  - head circumference/abdominal circumference ratio <10th percentile
  - femur length/abdominal circumference ratio <20th percentile

### Management
- prevent hyperglycemia in women with DM, optimize pre-pregnancy weight, and limit pregnancy weight gain
- prophylactic C/S is a reasonable option where EFW >5000 g in non-diabetic woman and EFW >4500 g in diabetic woman
- risks and benefits of early induction (risk of C/S vs. risk of dystocia) must be weighed in diabetic mothers, need for person-centred and shared decision-making

# Polyhydramnios/Oligohydramnios

**Table 11. Polyhydramnios and Oligohydramnios**

| | Polyhydramnios | Oligohydramnios |
|---|---|---|
| **Definition** | AFI >25 cm<br>U/S: single deepest pocket >8 cm | AFI <5 cm<br>U/S: single deepest pocket ≤2 cm |
| **Etiology** | Idiopathic most common<br>Maternal<br>Type 1 DM: abnormalities of transchorionic flow<br>Maternal-fetal<br>Chorioangiomas<br>Multiple gestation<br>Fetal hydrops (increased erythroblastosis)<br>Fetal<br>Chromosomal anomaly (up to 2/3 of fetuses have severe polyhydramnios)<br>Respiratory: cystic adenomatoid malformed lung<br>CNS: anencephaly, hydrocephalus, meningocele<br>GI: tracheoesophageal fistula, duodenal atresia, facial clefts (interfere with swallowing) | Idiopathic most common<br>Maternal<br>Uteroplacental insufficiency (preeclampsia, nephropathy)<br>Medications (ACEI)<br>Fetal<br>Congenital urinary tract anomalies (renal agenesis, obstruction, posterior urethral valves)<br>Demise/chronic hypoxemia (blood shunt away from kidneys to perfuse brain)<br>IUGR<br>Ruptured membranes: prolonged amniotic fluid leak<br>Amniotic fluid normally decreases after 35 wk |
| **Epidemiology** | Occur in 0.2-1.6% of all pregnancies | Occur in ~4.5% of all pregnancies<br>Severe form in <0.7%<br>Common in pregnancies >41 wk (~12%) |
| **Clinical Features and Complications** | Uterus large for dates, difficulty palpating fetal parts and hearing FHR<br>Maternal complications<br>Pressure symptoms from overdistended uterus (dyspnea, edema, hydronephrosis)<br>Obstetrical complications<br>Cord prolapse, placental abruption, malpresentation, preterm labour, uterine dysfunction, and PPH | Uterus small for dates<br>Fetal complications<br>15-25% have fetal anomalies<br>Amniotic fluid bands (T1) can lead to Potter's facies, limb deformities, abdominal wall defects<br>Obstetrical complications<br>Cord compression<br>Increased risk of adverse fetal outcomes<br>Pulmonary hypoplasia (late-onset)<br>Marker for infants who may not tolerate labour well |
| **Management** | Determine underlying cause<br>Screen for maternal disease/infection<br>Complete fetal U/S evaluation<br>Depends on severity<br>Mild to moderate cases require no treatment<br>If severe, hospitalize and consider therapeutic amniocentesis | Always warrants admission and investigation<br>Rule out ROM<br>Fetal monitoring (NST, BPP)<br>U/S Doppler studies (umbilical cord and uterine artery)<br>Maternal hydration with oral or IV fluids to help increase amniotic fluid<br>Injection of fluid via amniocentesis will improve condition for ~1 wk – may be most helpful for visualizing any associated fetal anomalies<br>Consider delivery if term<br>Amnio-infusion may be considered during labour via intrauterine catheter |
| **Prognosis** | 2-5 fold increase in risk of perinatal mortality | Poorer with early onset<br>High mortality related to congenital malformations and pulmonary hypoplasia when diagnosed during T2 |

# Multi-Fetal Gestation and Malpresentation



## Epidemiology

- incidence of twins is 1/80 and triplets 1/6400 in North America
- 2/3 of twins are dizygotic (fraternal)
  - risk factors for dizygotic twins: IVF, increased maternal age, newly discontinued OCP, and ethnicity (e.g. certain African regions)
- monozygous twinning occurs at a constant rate worldwide (1/250)
- determine zygosity by number of placentas, thickness of membranes, sex, and blood type

## Clinical Features

**Table 12. Complications Associated with Multiple Gestation**

| Maternal | Uteroplacental | Fetal |
|---|---|---|
| Hyperemesis gravidarum<br>GDM<br>Gestational HTN<br>Anemia<br>Increased physiological stress on all systems<br>Increased compressive symptoms<br>C/S | Increased PROM/PTL<br>Polyhydramnios<br>Placenta previa<br>Placental abruption<br>PPH (uterine atony)<br>Umbilical cord prolapse<br>Cord anomalies (velamentous insertion, 2 vessel cord) | Prematurity<br>IUGR<br>Malpresentation<br>Congenital anomalies<br>Twin-twin transfusion<br>Increased perinatal morbidity and mortality<br>Twin interlocking (twin A breech, twin B vertex)<br>Single fetal demise |

### Management
- U/S determination of chorionicity must be done within T1 (ideally 8-12 wk GA)
- increased antenatal surveillance
  - serial U/S q3-4wk from 22 wk GA to assess growth (uncomplicated diamniotic dichorionic)
  - increased frequency of U/S in monochorionic diamniotic and monochorionic monoamniotic twins
  - Doppler flow studies weekly if discordant fetal growth (>30%)
  - BPP as needed
- may attempt vaginal delivery if twin A presents as vertex, otherwise C/S (40-50% of all twin deliveries, 10% of cases have twin A delivered vaginally and twin B delivered by C/S)
- mode of delivery depends on fetal weights, GA, and presentation

**The Ps of Multiple Gestation Complications**

**Increased rates of**
**P**uking
**P**allor (anemia)
**P**reeclampsia/**P**IH
**P**ressure (compressive symptoms)
**P**TL/**P**ROM/**PP**ROM
**P**olyhydramnios
**P**lacenta previa/abruption
**P**PH/A**P**H
**P**rolonged labour
Cord **p**rolapse
**P**rematurity
Mal**p**resentation
**P**erinatal morbidity and mortality
**P**arental distress
**P**ostpartum depression

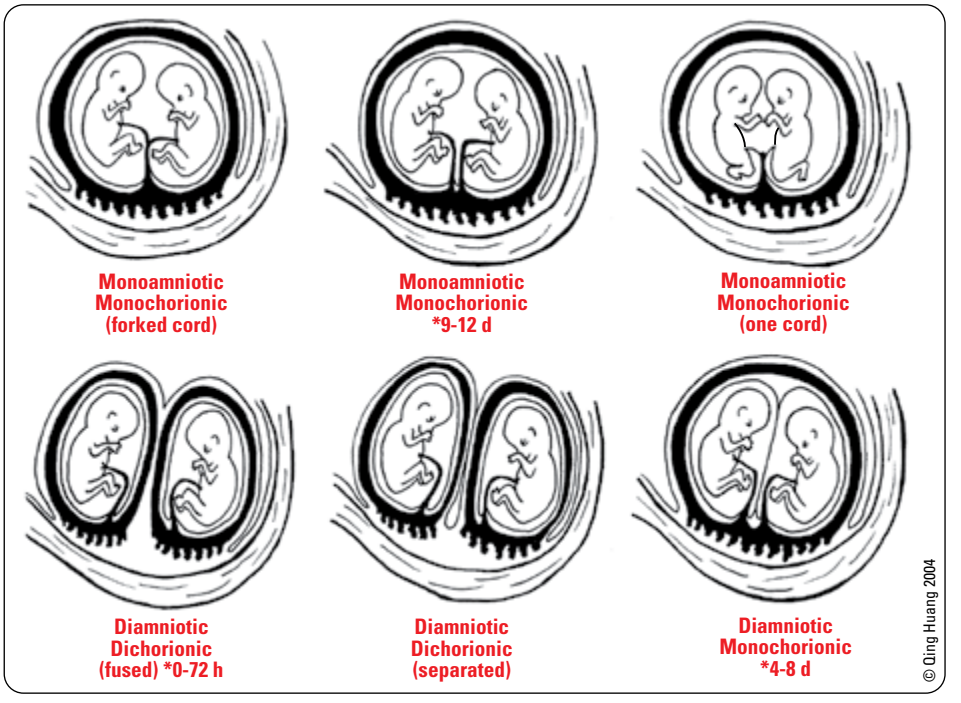



**Figure 4. Classification of twin pregnancies** ***Indicates time of cleavage**

## Twin-Twin Transfusion Syndrome

### Definition
- formation of placental intertwin vascular anastomoses causes arterial blood from donor twin to pass into veins of the recipient twin

### Epidemiology
- 10% of monochorionic twins
- concern if >30% discordance in estimated fetal weight

### Clinical Features
- donor twin: IUGR, hypovolemia, hypotension, anemia, and oligohydramnios
- recipient twin: hypervolemia, HTN, CHF, polycythemia, edema, polyhydramnios, and kernicterus in neonatal period

### Investigations
- detected by U/S screening, Doppler flow analysis

### Management
- therapeutic serial amniocentesis to decompress polyhydramnios of recipient twin and decrease pressure in cavity and on placenta
- intrauterine blood transfusion to donor twin if necessary
- laparoscopic occlusion of placental vessels
- fetoscopic laser ablation of placental vascular anastomoses when indicated and if available

# Breech Presentation

## Definition
- fetal buttocks or lower extremity is the presenting part as determined on U/S
- complete (10%): hips and knees both flexed
- frank (60%): hips flexed, knees extended, buttocks present at cervix
  - most common type of breech presentation
  - most common breech presentation to be delivered vaginally
- incomplete (30%): both or one hip partially flexed and both or one knee present below the buttocks, feet or knees present first (footling breech, kneeling breech)

## Epidemiology
- occurs in 3-4% of pregnancies at term (25% <28 wk)

## Risk Factors
- maternal: pelvis (contracted), uterus (shape abnormalities, intrauterine tumours, fibroids, previous breech), pelvic tumours causing compression, and grand multiparity
- placental: placenta previa
- fetal: prematurity, amniotic fluid (poly-/oligohydramnios), multiple gestation, congenital malformations (found in 6% of breeches; 2-3% if in vertex presentations), abnormalities in fetal tone and movement, aneuploidy, hydrocephalus, and anencephalus

## Management
- ECV (external cephalic version): repositioning of singleton fetus within uterus under U/S guidance
  - overall success rate of ~60%
  - criteria: >36 wk GA, singleton, unengaged presenting part, reactive NST, not in labour
  - absolute contraindications: where C/S is required (placenta previa, previous classical C/S), previous myomectomy, PROM, uteroplacental insufficiency, nuchal cord, non-reactive NST, multiple gestation
  - relative contraindications: mild/moderate oligohydramnios, suspected IUGR, HTN, previous T3 bleed
  - risks: abruption, cord compression, cord accident, ROM, labour, fetal bradycardia requiring C/S (<1% risk), alloimmunization, fetal death (1:5000)
  - method: tocometry, followed by U/S guided transabdominal manipulation of fetus with constant fetal heart monitoring
  - if patient Rh negative, give Rhogam® after the procedure
  - better prognosis if multiparous, good fluid volume, small baby, skilled obstetrician, and posterior placenta
- pre-or early-labour U/S to assess type of breech presentation, fetal growth, estimated weight, placenta position, attitude of fetal head (flexed is preferable); if U/S unavailable, recommend C/S
- ECV and elective C/S should be presented as options with the risks and benefits outlined; obtain informed consent
- method for vaginal breech delivery
  - encourage effective maternal pushing efforts
  - at delivery of head (after feet), assistant must apply suprapubic pressure to flex and engage fetal head
  - delivery can be spontaneous or assisted; avoid fetal traction
  - apply fetal manipulation only after spontaneous delivery to level of umbilicus
- contraindications to vaginal breech delivery
  - cord presentation
  - clinically inadequate maternal pelvis
  - fetal factors incompatible with vaginal delivery (e.g. hydrocephalus, macrosomia, fetal growth restriction)
- C/S recommended if: the breech has not descended to the perineum in the second stage of labour after 2 h, in the absence of active pushing, or if vaginal delivery is not imminent after 1 h of active pushing

## Prognosis
- regardless of route of delivery, breech infants have lower birth weights and higher rates of perinatal mortality, congenital anomalies, abruption, and cord prolapse

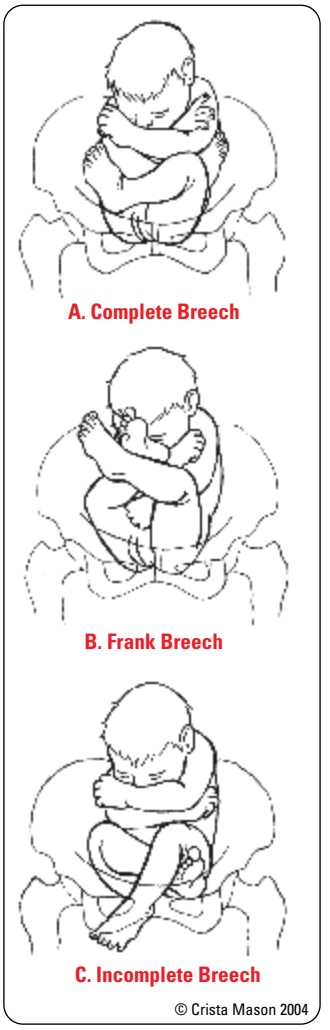



**Figure 5. Types of breech presentation**

**Criteria for Vaginal Breech Delivery**
- Frank or complete breech, GA >36 wk
- EFW 2500-3800 g based on clinical and U/S assessment (5.5–8.5 lb)
- Fetal head flexed
- Continuous fetal monitoring
- 2 experienced obstetricians, assistant, and anesthetist present
- Ability to perform emergency C/S within 30 min if required

# Hypertensive Disorders of Pregnancy

## Hypertension in Pregnancy

- hypertensive disorders of pregnancy are classified as either pre-existing or gestational HTN. Pre-eclampsia and eclampsia are included in the spectrum of hypertensive disorders of pregnancy

**Ominous Symptoms of HTN in Pregnancy**
RUQ pain, headache, and visual disturbances

### PRE-EXISTING HYPERTENSION

#### Definition
- BP ≥140/90 prior to 20 wk GA; BP should be elevated on ≥2 occasions at least 15 minutes apart
- essential HTN is associated with an increased risk of gestational HTN, abruptio placentae, IUGR, and IUFD

### GESTATIONAL HTN

#### Definition
- sBP ≥140 or dBP ≥90 after 20 wk GA without proteinuria in a woman known to be normotensive before pregnancy

### PREECLAMPSIA
#### Definition
- pre-existing or gestational HTN with new onset proteinuria or adverse conditions (end organ dysfunction)

### ECLAMPSIA
#### Definition
- the occurrence of ≥1 generalized convulsions and/or coma in the setting of preeclampsia and in the absence of other neurologic conditions

**Note**
Eclampsia prior to 20 wk of gestation is rare and should raise the possibility of an underlying molar pregnancy or antiphospholipid syndrome

#### Epidemiology of Eclampsia
- an eclamptic seizure occurs in approximately 0.5% of mildly preeclamptic women and 2-3% of severely preeclamptic women

#### Clinical Manifestation of Eclampsia
- eclampsia is a clinical diagnosis
- typically tonic-clonic and lasting 60-75 s
- symptoms that may occur before the seizure include persistent frontal or occipital headache, blurred vision, photophobia, right upper quadrant or epigastric pain, and altered mental status
- in up to one third of cases, there is no proteinuria or blood pressure >140/90 mmHg prior to the seizure
- in general, women with typical eclamptic seizures who do not have focal neurologic deficits or prolonged coma do not require diagnostic evaluation including imaging

#### Risk Factors for Hypertensive Disorders in Pregnancy
- maternal factors
  - primigravida (80-90% of gestational HTN), first conception with a new partner, PMHx or FHx of gestational HTN, or preeclampsia/eclampsia
  - DM, chronic HTN, or renal insufficiency
  - obesity
  - antiphospholipid syndrome or inherited thrombophilia
  - extremes of maternal age (<18 or >35 yr)
  - previous stillbirth or IUFD
  - vascular or connective tissue disease
- fetal factors
  - IUGR or oligohydramnios
  - GTN
  - multiple gestation
  - fetal hydrops "mirror syndrome"
  - abruptio placentae

**Hypertension in Pregnancy**

**Adverse Maternal Conditions**
- sBP >160 mmHg
- dBP >100 mmHg
- HELLP
- Cerebral hemorrhage
- Renal dysfunction: oliguria <500 mL/d
- Left ventricular failure, pulmonary edema
- Placental abruption, DIC
- **Symptoms**
  - Abdominal pain, N/V
  - Headaches, visual problems
  - SOB, chest pain
  - Eclampsia: convulsions

**Adverse Fetal Conditions**
- IUGR
- Oligohydramnios
- Absent/reversed umbilical artery end diastolic flow
- **Can result in:**
  - Fetal disability and/or death

#### Clinical Evaluation of Hypertensive Disorders in Pregnancy
- in general, clinical evaluation should include the mother and fetus
- evaluation of mother:
  - body weight
  - central nervous system
    - presence and severity of headache
    - visual disturbances – blurring, scotomata

        - tremulousness, irritability,and somnolence
        - hyperreflexia
    - hematologic
        - bleeding, petechiae
    - hepatic
        - RUQ or epigastric pain
        - severe N/V
    - renal
        - urine output and colour
- evaluation of fetus:
    - fetal movement
    - fetal heart rate tracing – NST
    - U/S for growth
    - BPP
    - Doppler flow studies

## Laboratory Evaluation of Hypertensive Disorders in Pregnancy

- CBC
- PTT, INR, fibrinogen – if abnormal LFTs or bleeding
- ALT, AST
- creatinine, uric acid
- 24 h urine collection for protein or albumin:creatinine ratio
- may consider placental growth factor (PlGF) testing as an early screening test for suspected preeclampsia

## Complications of Hypertensive Disorders in Pregnancy

- maternal
    - liver and renal dysfunction
    - seizure - "eclampsia"
    - abruptio placentae
    - left ventricular failure/pulmonary edema
    - DIC (release of placental thromboplastin consumptive coagulopathy)
    - HELLP syndrome
    - hemorrhagic stroke (50% of deaths)
- fetal (2° to placental insufficiency)
    - IUGR, prematurity, abruptio placentae, IUFD

## Management of HTN

- for non-severe HTN (149-159/90-105) target a BP of 130-155/80-105 in women without comorbidities or <140/90 in women with comorbidities
- for both pre-existing and gestational HTN, labetalol 100-400 mg PO bid-tid, nifedipine XL preparation 20-60 mg PO od, or α-methyldopa 250-500 mg PO bid-qid
- for severe HTN (BP>160/110), give one of:
    - labetalol 20 mg IV then 20-80 mg IV q30min (max 300 mg) (then switch to oral)
    - nifedipine 5-10 mg capsule q30min
        - hydralazine 5 mg IV, repeat 5-10 mg IV q30min or 0.5 to 10 mg/h IV, to a maximum of 20 mg IV (or 30 mg IM)
- no ACEI, ARBs, diuretics (in cases of pulmonary edema or cardiac failure, may be used), prazosin, or atenolol
- pre-existing HTN and gestational HTN without any deterioration can be followed until 37 wk, then decide to induce shortly thereafter

## Management of Preeclampsia

- if stable and no adverse factors (GA 24-33+6 wk), expectant management, ± delivery as approaching 34-36 wk (must weigh risks of fetal prematurity vs. risks of developing severe preeclampsia/eclampsia)
- antenatal corticosteroids should be considered if GA ≤ 34 wk
- if >37 wk, immediate delivery is recommended
- for severe preeclampsia, stabilize and deliver, regardless of GA
- if severe preeclampsia during labour, increase maternal monitoring: hourly input and output, urine dip q12h, hourly neurological vitals, and increase fetal monitoring (continuous FHR monitoring)
- antihypertensive therapy
    - labetalol 20 mg IV, then 20-80 mg IV q30min (max 300 mg) (then switch to oral)
    - nifedipine 5-10 mg capsule q30min
        - hydralazine 5 mg IV, repeat 5-10 mg IV q30min or 0.5-10 mg/h IV, to a maximum of 20 mg IV (or 30 mg IM)



**I-A Evidence-Recommendation Highlights of SOGC Clinical Practice Guidelines Diagnosis, Evaluation, and Management of the Hypertensive Disorders of Pregnancy**
J Obstet Gynaecol Can 2014;36(5):416-38

- For BP measurement, Korotkoff phase V should be used to designate the dBP.
- Calcium supplementation (of at least 1g/d, orally) is recommended for women with low dietary intake of calcium (<600 mg/d). (I-A)
- For preeclampsia prevention among increased risk women, low-dose ASA (75-100 mg/d) is recommended until delivery.
- Umbilical artery Doppler velocimetry should be part of the antenatal fetal surveillance in preeclampsia.
- Initial antihypertensive therapy for severe HTN (sBP >160 or dBP ≥110) should be with labetalol, nifedipine, or hydralazine.
- Initial antihypertensive therapy for non-severe HTN (BP 140-159/90-109 mmHg) should be with methyldopa, β-blockers, or calcium channel blockers.
- Antenatal corticosteroids for fetal lung maturation should be considered for all women with preeclampsia before 34 wk gestation.
- In a planned vaginal delivery with an unfavourable cervix, cervical ripening should be used.
- Oxytocin 5 units IV or 10 units IM should be used as part of the management during the third stage of labour, particularly in the presence of thrombocytopenia or coagulopathy.
- Magnesium sulfate is the recommended first-line treatment for eclampsia.
- Magnesium sulfate is the recommended eclampsia prophylaxis in severe preeclampsia.





**Preeclampsia Investigations**

- CBC
- AST, ALT
- INR and aPTT (if abn LFTs or bleeding)
- Cr
- Urine (24 h protein collection or albumin/creatinine ratio)
- Uric acid

- seizure prevention
  - magnesium sulfate: 4 g IV loading dose, followed by 1g/h
  - postpartum management
  - risk of seizure highest in first 24 h postpartum – continue $MgSO_4$ for 12-24 h after delivery
  - vitals q1h
  - consider HELLP syndrome
  - most return to a normotensive BP within 2 wk

### Management of Eclampsia

- ABCs
- roll patient into LLDP
- supplemental $O_2$ via face mask to treat hypoxemia due to hypoventilation during convulsive episode
- aggressive antihypertensive therapy for sustained dBP ≥105 mmHg or sBP ≥160 mmHg with hydralazine or labetalol
- prevention of recurrent convulsions: to prevent further seizures and the possible complications of repeated seizure activity (e.g. rhabdomyolysis, metabolic acidosis, aspiration pneumonitis, etc.)
- $MgSO_4$ is now the drug of choice
- the definitive treatment of eclampsia is DELIVERY, irrespective of gestational age, to reduce the risk of maternal morbidity and mortality from complications of the disease
- mode of delivery is dependent on clinical situation and fetal-maternal condition

**HELLP Syndrome**
**H**emolysis
**E**levated **L**iver Enzymes
**L**ow Platelets

**Differential Diagnosis of Cause for Seizure in a Pregnant Woman**
- Stroke
- Hypertensive disease (hypertensive encephalopathy, pheochromocytoma)
- Space-occupying lesion of the CNS
- Metabolic disorders (hypoglycemia, SIADH)
- Infection (meningitis, encephalitis)
- TTP or thrombophilia
- Idiopathic epilepsy
- Use of illicit drugs
- Cerebral vasculitis

# Medical Complications of Pregnancy

## Iron and Folate Deficiency Anemia

**Table 13. Iron Deficiency and Folate Deficiency Anemia**

| | Iron Deficiency Anemia | Folate Deficiency Anemia |
|---|---|---|
| **Etiology** | See Hematology, H15 | See Hematology, H25 |
| **Epidemiology** | Responsible for 80% of non-physiologic anemia during pregnancy | Incidence varies from 0.5-25% depending on region, population, and diet |
| **Clinical Features** | See Hematology, H15 | See Hematology, H25 |
| **Investigations** | See Hematology, H15 | See Hematology, H25 |
| **Management** | Prevention (non-anemic): 30 mg elemental iron/d (met by most prenatal vitamins)<br>Treatment (anemic): 30-120 mg elemental iron/d<br>325 mg ferrous fumarate = 106 mg elemental Fe; 325 mg ferrous sulfate = 65 mg elemental Fe; 325 mg ferrous gluconate = 36 mg elemental Fe<br>Polysaccharide-Iron Complex = 150 mg elemental Fe/capsule | Prevention: 0.4-1 mg folic acid PO daily for 1-3 mo preconceptually and throughout T1, or 5 mg folic acid/d with past history of ONTD, DM, or antiepileptic medication use |
| **Complications** | Maternal: angina, CHF, infection, slower recuperation, preterm labour<br>Fetal: decreased oxygen carrying capacity leading to fetal distress, IUGR, and low birth weight | Maternal: decreased blood volume, N/V, and anorexia<br>Fetal: neural tube defects in T1, low birth weight, and prematurity |
| **Notes** | Mother needs 1 g of elemental iron per fetus; this amount exceeds normal stores + dietary intake<br>Iron requirements increase during pregnancy due to fetal/placental growth (500 mg), increased maternal RBC mass (500 mg), and losses (200 mg) – more needed for multiple gestations | Minimum daily requirement is 0.4 mg<br>Most often associated with iron deficiency anemia<br>Folic acid is necessary for closure of neural tube during early fetal development (by day 28 of gestation) |

## Diabetes Mellitus

### Epidemiology

- 2-4% of pregnancies are complicated by DM

### Classification of Diabetes Mellitus

- type 1 and type 2 DM (see Endocrinology, E7)
- GDM: onset of DM during pregnancy (usually tested for around 24-28 wk GA)

### Etiology

- type 1 and type 2 DM
- GDM: anti-insulin factors produced by placenta and high maternal cortisol levels create increased peripheral insulin resistance → leading to GDM and/or exacerbating pre-existing DM

## MANAGEMENT

### A. TYPE 1 and TYPE 2 DM

#### Preconception
- pre-plan and refer to high-risk clinic
- commence folic acid 3 mo prior
- optimize glycemic control (HbA1c <6%)
- counsel patient on potential risks and complications
- evaluate for diabetic retinopathy, neuropathy, and CAD

#### Pregnancy
- for Type 2 DM, if already on oral medication, generally switch to insulin therapy
  - continuing glyburide or metformin controversial
  - teratogenicity unknown for other oral anti-hyperglycemics
- tight glycemic control
  - insulin dosage may need to be adjusted in T2 due to increased demand and increased insulin resistance
- monitor as for normal pregnancy, plus initial 24 h urine protein and creatinine clearance, retinal exam, and HbA1c
  - HbA1c: >140% of pre-pregnancy value associated with increased risk of spontaneous abortion and congenital malformations
- increased fetal surveillance (fetal growth, BPP, NST) starting in the late T2 and T3, consider fetal ECHO in the T2 (if high HbA1c in T1 or just prior to pregnancy) to look for cardiac abnormalities

**Monitoring Glucose Levels**
- Frequent measurements of blood glucose during pregnancy are advised for women with type 1 or 2 DM to help prevent or treat both hypoglycemia and hyperglycemia, and also improves neonatal outcome
- Aim for:
  - FPG ≤5.3 mmol/L (95 mg/dL)
  - 1 h post prandial PG ≤7.8 mmol/L (140 mg/dL), 2 h post prandial PG ≤6.7 mmol/L (120 mg/dL)
- Most women can be followed with monthly HbA1c determinations

#### Labour
- timing of delivery depends on fetal and maternal health and risk factors (i.e. must consider size of baby, lung maturity, maternal blood glucose)
- induce by 38-39 wk, depending on glycemic control and presence of end-organ involvment
- type of delivery
  - increased risk of cephalopelvic disproportion (CPD) and shoulder dystocia with babies >4000 g (8.8 lbs)
  - consider elective C/S for predicted birthweight >4500 g (9.9 lbs) (controversial)
- monitoring
  - during labour, monitor blood glucose q1h with patient on insulin and dextrose drip
  - aim for blood glucose between 3.9-7 mmol/L to reduce the risk of neonatal hypoglycemia

Post-prandial blood glucose values seem to be the most effective at determining the likelihood of macrosomia or other adverse pregnancy outcomes

#### Postpartum
- insulin requirements dramatically drop with expulsion of placenta (source of insulin antagonists)
- monitor glucose q6h, restart insulin at two-thirds of pre-pregnancy dosage when glucose >8 mmol/L

### B. GESTATIONAL DM

#### Screening and Diagnosis
- all pregnant women between 24-28 wk GA (or at any stage if high risk)
- 2 screening options
  - 2-step screening (recommended by the Canadian Diabetes Association)
    - Step 1: perform a random non-fasting 50 g OGCT
      - 1 h PG <7.8 mmol/L is normal
      - 1 h PG ≥11.1 mmol/L is GDM
      - if 1 h PG 7.8-11.0 mmol/L, proceed to Step 2
    - Step 2: perform a fasting 75 g OGTT, GDM if ≥1 of:
      - FPG ≥5.3 mmol/L
      - 1 h PG ≥10.6 mmol/L
      - 2 h PG ≥9.0 mmol/L
  - Alternative 1-step screening with fasting 75 g OGTT; GDM if ≥1 of:
    - FPG ≥5.1 mmol/L
    - 1 h PG ≥10.0 mmol/L
    - 2 h PG ≥8.5 mmol/L

**Risk Factors for GDM**
- Age >25 yr
- Obesity
- Ethnicity (Aboriginal, Hispanic, Asian, and African)
- FHx of DM
- Previous history of GDM
- Previous child with birthweight >4.0 kg
- Polycystic ovarian syndrome
- Current use of glucocorticoids
- Essential HTN or pregnancy-related HTN

#### Management
- first line: diet modification and increased physical activity
- initiate insulin therapy if glycemic targets not achieved within 2 wk of lifestyle modification alone
- glycemic targets: FPG <5.3 mmol/L, 1 h PG <7.8 mmol/L, 2 h PG <6.7 mmol/L
- oral agents can be used in pregnancy but is off-label and should be discussed with patient
- stop insulin and diabetic diet postpartum
- follow-up with 75 g OGTT between 6 wk-6 mo postpartum, counsel about lifestyle modifications

#### Prognosis
- most maternal and fetal complications are related to hyperglycemia and its effects

**Table 14. Complications of DM in Pregnancy**

| Maternal | Fetal |
|---|---|
| **Obstetric**<br>HTN/preeclampsia (especially if pre-existing nephropathy/proteinuria): insulin resistance is implicated in etiology of HTN<br>Polyhydramnios: maternal hyperglycemia leads to fetal hyperglycemia, which leads to fetal polyuria (a major source of amniotic fluid) | **Growth Abnormalities**<br>Macrosomia: maternal hyperglycemia leads to fetal hyperinsulinism resulting in accelerated anabolism<br>IUGR: due to placental vascular insufficiency |
| **Diabetic Emergencies**<br>Hypoglycemia<br>Ketoacidosis<br>Diabetic coma | **Delayed Organ Maturity**<br>Fetal lung immaturity: hyperglycemia interferes with surfactant synthesis (respiratory distress syndrome) |
| **End-Organ Involvement or Deterioration (occur in type 1 DM and type 2 DM, not in GDM)**<br>Retinopathy<br>Nephropathy | **Congenital Anomalies (occur in type 1 DM and type 2 DM, not in GDM)**<br>2-7x increased risk of cardiac (ventricular septal defect), NTD, GU (cystic kidneys), GI (anal atresia), and MSK (sacral agenesis) anomalies due to hyperglycemia<br>Note: Pregnancies complicated by GDM do not manifest an increased risk of congenital anomalies because GDM develops after the critical period of organogenesis (in T1) |
| **Other**<br>Pyelonephritis/UTI: glucosuria provides a culture medium for *E. coli* and other bacteria<br>Increased incidence of spontaneous abortion (in type 1 DM and type 2 DM, not in GDM): related to pre-conception glycemic control | **Labour and Delivery**<br>Preterm labour/prematurity: most commonly in patients with HTN/preeclampsia<br>Preterm labour is associated with poor glycemic control but the exact mechanism is unknown<br>Increased incidence of stillbirth<br>Birth trauma: due to macrosomia, can lead to difficult vaginal delivery and shoulder dystocia<br><br>**Neonatal**<br>Hypoglycemia: due to pancreatic hyperplasia and excess insulin secretion in the neonate<br>Hyperbilirubinemia and jaundice: due to prematurity and polycythemia<br>Hypocalcemia: exact pathophysiology not understood, may be related to functional hypoparathyroidism<br>Polycythemia: hyperglycemia stimulates fetal erythropoietin production |

### Long-Term Maternal Complications
- type 1 and type 2 DM: risk of progressive retinopathy and nephropathy
- GDM: 50% risk of developing type 2 DM in next 20 yr

## Early-Onset Group B *Streptococcus*

### Epidemiology
- 15-40% recto-vaginal carrier rate

### Risk Factors (for neonatal disease)
- maternal intrapartum GBS colonization during current pregnancy
- GBS bacteria at any time during the current pregnancy
- previous infant with invasive GBS disease
- prolonged rupture of membranes ≥18 h
- maternal fever (temperature ≥38°C)

### Clinical Features
- not harmful to mother
- risk of vertical transmission (neonatal sepsis, meningitis or pneumonia, and death)

### Investigations
- offer screening to all women at 35-37 wk with vaginal and anorectal swabs for GBS culture

### Treatment
- prophylactic treatment of maternal GBS at delivery decreases neonatal morbidity and mortality
- indications for antibiotic prophylaxis: positive GBS screen, GBS in urine, previous infant with GBS disease, or GBS status unknown + one of the other risk factors
- antibiotics for GBS prophylaxis (should be given 4 h prior to delivery to be considered adequate)
  - penicillin G, 5 million IU IV, then 2.5 million IU IV q4h until delivery
  - penicillin allergic but not at risk for anaphylaxis: cefazolin 2 g IV then 1 g q8h
  - penicillin allergic and at risk of anaphylaxis: vancomycin 1 g IV q12h until delivery (vancomycin and clindamycin levels in amniotic fluid do not reach therapeutic levels, all babies should be screened for GBS despite treatment)
- if maternal fever, broad spectrum antibiotic coverage is advised



**Indications for Intrapartum Antibiotic GBS Prophylaxis**
Centres for Disease Control and Prevention. Prevention of Perinatal Group B Streptococcal Disease. MMWR 2010;59(RR-10):14
- Previous infant with invasive GBS disease
- GBS bacteriuria during any trimester of the current pregnancy
- Positive GBS vaginal-rectal screening culture in late gestation during current pregnancy
- Unknown GBS status at the onset of labour (culture not done, incomplete, or results unknown) and any of the following:
  - Delivery at <37 wk gestation
  - Amniotic membrane rupture ≥18 h
  - Intrapartum temperature ≥38.0 °C (≥100.4 °F)
  - Intrapartum nucleic-acid amplification test positive for GBS

# Urinary Tract Infection

## Epidemiology
- most common medical complication of pregnancy
- asymptomatic bacteriuria in 2-7% of pregnant women, more frequently in multiparous women
- note: asymptomatic bacteriuria should be treated in pregnancy due to increased risk of pyelonephritis and preterm labour

Treat asymptomatic bacteriuria in pregnancy because of increased risk of progression to cystitis, pyelonephritis, and probable increased risk of preterm labour

## Etiology
- increased urinary stasis from mechanical and hormonal (progesterone) factors
- organisms include GBS as well as those that occur in non-pregnant women

## Clinical Features
- may be asymptomatic
- dysuria, urgency, and frequency in cystitis
- fever, flank pain, and costovertebral angle tenderness in pyelonephritis

## Investigations
- urinalysis, urine C&S
- cystoscopy and renal function tests in recurrent infections

## Management
- uncomplicated UTI
  - first line: amoxicillin (250-500 mg PO q8h x 7 d)
  - alternatives: nitrofurantoin (100 mg PO bid x 7 d) or cephalosporins
  - follow with monthly urine cultures
- pyelonephritis
  - hospitalization and IV antibiotics

## Prognosis
- complications if untreated: acute cystitis, pyelonephritis, and possible preterm labour
- recurrence is common

# Infections During Pregnancy

**Table 15. Infections During Pregnancy**

| Infection | Agent | Source of Transmission | Greatest Transmission Risk to Fetus | Effects on Fetus | Effects on Mother | Diagnosis | Management |
|---|---|---|---|---|---|---|---|
| **Chicken Pox** | Varicella zoster virus (herpes family) | To mother: direct, respiratory<br>To baby: transplacental | 13-30 wk GA, and 5 d pre- to 2 d post-delivery | Congenital varicella syndrome (limb aplasia, chorioretinitis, cataracts, cutaneous scars, cortical atrophy, IUGR, hydrops), preterm labour | Fever, malaise, vesicular pruritic lesions | Clinical, ± vesicle fluid culture, ± serology | Varicella-zoster immune globulin for mother if exposed, decreases congenital varicella syndrome<br>Note: do not administer vaccine during pregnancy (live attenuated vaccine) |
| ***Cytomegalovirus** | DNA virus (herpes family) | To mother: blood/ organ transfusion, sexual contact<br>To baby: transplacental, during delivery, breast milk | T1-T3 | 5-10% develop CNS involvement (mental retardation, cerebral calcification, hydrocephalus, microcephaly, deafness, chorioretinitis) | Asymptomatic or flu-like | Serologic screen; isolate virus from urine or secretion culture | No specific treatment; maintain good hygiene and avoid high risk situations |
| **Erythema Infectiosum (Fifth Disease)** | Parvovirus B19 | To mother: respiratory, infected blood products<br>To baby: transplacental | 10-20 wk GA | Spontaneous abortion (SA), stillbirth, hydrops *in utero* | Flu-like, rash, arthritis; often asymptomatic | Serology, viral PCR, maternal AFP; if IgM present, follow fetus with U/S for hydrops | If hydrops occurs, consider fetal transfusion |
| **Hepatitis B** | DNA virus | To mother: blood, saliva, semen, vaginal secretions<br>To baby: transplacental, breast milk | T3<br>10% vertical transmission if asymptomatic and HBsAg +ve; 85-90% if HBsAg and HBeAg +ve | Prematurity, low birth weight, neonatal death | Fever, N/V, fatigue, jaundice, elevated liver enzymes | Serologic screening for all pregnancies | Rx neonate with HBIG and vaccine (at birth, 1, 6 mo); 90% effective |
| ***Herpes Simplex Virus** | DNA virus | To mother: intimate mucocutaneous contact<br>To baby: transplacental, during delivery | Delivery (if genital lesions present); less commonly *in utero* | Disseminated herpes (20%); CNS sequelae (35%); self-limited infection | Painful vesicular lesions | Clinical diagnosis | Acyclovir for symptomatic women, suppressive therapy at 36 wk controversial<br>Suggested C/S if active genital lesions, even if remote from vulva |

**Table 15. Infections During Pregnancy** (continued)

| Infection | Agent | Source of Transmission | Greatest Transmission Risk to Fetus | Effects on Fetus | Effects on Mother | Diagnosis | Management |
|---|---|---|---|---|---|---|---|
| **HIV** | RNA retrovirus | To mother: blood, semen, vaginal secretions<br>To baby: in utero, during delivery, breast milk | 1/3 *in utero*, 1/3 at delivery, 1/3 breastfeeding | IUGR, preterm labour, PROM | See Infectious Diseases, ID25 | Serology, viral PCR<br>All pregnant women are offered screening | Triple anti-retroviral therapy decreases transmission to <1%<br>Elective C/S: no previous antiviral Rx or monotherapy only, viral load unknown or >500 RNA copies/mL, unknown prenatal care, patient request |
| ***Rubella** | ssRNA togavirus | To mother: respiratory droplets (highly contagious)<br>To baby: transplacental | T1 | SA or congenital rubella syndrome (hearing loss, cataracts, CV lesions, mitral regurgitation, IUGR, hepatitis, CNS defects, osseous changes) | Rash (50%), fever, posterior auricular or occipital lymphadenopathy, arthralgia | Serologic testing; all pregnant women screened (immune if titre >1:16); infection if IgM present or >4x increase in IgG | No specific treatment; offer vaccine following pregnancy<br>Do not administer during pregnancy (live attenuated) |
| **Syphilis** | Spirochete (*Treponema pallidum*) | To mother: sexual contact<br>To baby: transplacental | T1-T3 | Risk of preterm labour, multisystem involvement, fetal death | See Infectious Diseases, ID23 | VDRL screening for all pregnancies; if positive, requires confirmatory testing | Penicillin G 2.4 million IU IM x 1 dose if early syphilis, 3 doses if late syphilis, monitor VDRL monthly<br>If penicillin G allergic: clindamycin 900 mg IV q8h |
| ***Toxoplasmosis** | Protozoa (*Toxoplasma gondii*) | To mother: raw meat, unpasteurized goat's milk, cat feces/urine<br>To baby: transplacental | T3 (but most severe if infected in T1); only concern if primary infection during pregnancy | Congenital toxoplasmosis (chorioretinitis, hydrocephaly, intracranial calcification, mitral regurgitation, microcephaly) NB: 75% initially asymptomatic at birth | Majority subclinical; may have flu-like symptoms | IgM and IgG serology; PCR of amniotic fluid | Self-limiting in mother; spiramycin decreases fetal morbidity but not rate of transmission |

* Indicates TORCH infection

# Venous Thromboembolism

## Epidemiology

- incidence of 12.1/10,000 (DVT), and 5.4/10,000 (PE)
- increased risk of VTE throughout pregnancy with highest risk of DVT in T3 and post-partum period; highest risk of PE post-partum (first 6 wk)

## Risk Factors

- previous VTE, age >35, obesity, infection, bedrest/immobility, shock/dehydration, and thrombophilias (see Hematology, H35)

**Table 16. Risk Factors for VTE Specific to Pregnancy**

| Hypercoagulability | Stasis | Endothelial |
|---|---|---|
| Increased Factors:<br>II, V, VII, VIII, IX, X, XII, fibrinogen<br>Increased platelet aggregation<br>Decreased protein S, tPA, factors XI, XIII<br>Increased resistance to activated protein C<br>Antithrombin can be normal or reduced | Increased venous distensibility<br>Decreased venous tone<br>50% decrease in venous flow in lower extremity by T3<br>Uterus is mechanical impediment to venous return | Vascular damage at delivery (C/S or SVD)<br>Uterine instrumentation<br>Peripartum pelvic surgery |



**Virchow's Triad for VTE**
- Hypercoagulable state
- Stasis
- Endothelial damage

## Clinical Features

- most DVTs occur in the iliofemoral or calf veins with a predilection for the left leg
- signs of a pulmonary embolism are non-specific

## Investigations

- duplex venous Doppler sonography for DVT
- CXR and V/Q scan or spiral CT for PE

## Management

- before initiating treatment, obtain a baseline CBC including platelets and aPTT
- treatment with LMWH preferred
  - dosing varies depending on specific LMWH used
  - should be discontinued at least 24 h prior to delivery

- unfractionated heparin
  - bolus of 5000 IU followed by an infusion of ~30,000 IU/24h
  - measure aPTT 6 h after the bolus
  - maintain aPTT at a therapeutic level (1.5-2x normal)
  - repeat q24h once therapeutic
  - heparin-induced thrombocytopenia (HIT) uncommon (3%), but serious complication
- warfarin is contraindicated during pregnancy due to its potential teratogenic effects
- compression stockings
- poor evidence to support a recommendation for or against avoidance of prolonged sitting
- VTE prophylaxis
  - women on long-term anticoagulation: full therapeutic anticoagulation throughout pregnancy and for 6-12 wk postpartum
  - women with a non-active PMHx of VTE: unfractionated heparin regimens suggested
  - insufficient evidence in pregnancy to recommend routine use of LMWH for all patients
  - current prophylaxis regimens for acquired thrombophilias (e.g. APS) include low dose ASA in conjunction with prophylactic heparin

# Normal Labour and Delivery

## Definition of Labour

- true labour: regular, painful contractions of increasing intensity associated with progressive dilatation and effacement of cervix and descent of presenting part, or progression of station
  - preterm (≥20 to ≤36+6 wk GA)
  - term (37-41+6 wk GA)
  - postterm (≥42 wk GA)
- false labour (Braxton-Hicks contractions): irregular contractions, with unchanged intensity and long intervals, occur throughout pregnancy and not associated with any cervical dilatation, effacement, or descent
  - often relieved by rest or sedation

## The Cervix

- see Bishop Score (see Table 21, OB37)
  - dilatation: latent phase (0-4 cm, variable time); active phase (4-10 cm)
  - effacement: thinning of the cervix by percentage or length of cervix (cm)
  - consistency: firm, medium, or soft
  - position: posterior, mid, or anterior
- other consideration:
  - application: contact between the cervix and presenting part (i.e. well or poorly applied)

## The Fetus

- **fetal lie**: orientation of the long axis of the fetus with respect to the long axis of the uterus (longitudinal, transverse, and oblique)
- **fetal presentation**: fetal body part closest to the birth canal
  - breech (complete, frank, and incomplete) (see Figure 5, OB23)
  - cephalic (vertex/occiput, face, or brow)
  - transverse (shoulder)
  - compound (fetal extremity prolapses along with presenting part)
  - all except vertex are considered malpresentations (see *Obstetrical Complications*, OB16)
- **fetal position**: position of presenting part of the fetus relative to the maternal pelvis
  - OA: most common presentation ("normal") – left OA most common
  - OP: most rotate spontaneously to OA; may cause prolonged second stage of labour
  - OT: leads to arrest of dilatation
    - normally, fetal head enters maternal pelvis and engages in OT position
    - subsequently rotates to OA position (or OP in a small percentage of cases)
- **attitude**: flexion/extension of fetal head relative to shoulders
  - brow presentation: head partially extended (requires C/S)
  - face presentation: head fully extended
    - mentum posterior always requires C/S, mentum anterior can deliver vaginally
- **station**: position of presenting bony part relative to ischial spines – determined by vaginal exam
  - at ischial spines = station 0 = engaged
  - –5 to –1 cm above ischial spines
  - +1 to +5 cm below ischial spines
- **asynclitism**: alignment of the sagittal suture relative to the axis of the birth canal
  - lateral tilt seen with either anterior or posterior asynclitism and may impact descent



**Maternal Triage Assessment**
**ID**: Age, GPA, EDD, GA, GBS, Rh, Serology
**CC**
**HPI**: 4 key questions:
- Contractions: Since when, how close (q x min), how long (x s), how painful
- Bleeding: Since when, how much (pads), colour (pinky vs. brownish vs. bright red), pain, last U/S, trauma/intercourse
- Fluid (ROM): Since when, large gush vs. trickle, soaked pants, clear vs. green vs. red, continuous
- FM: As much as usual?, When last movement?, Kick counts (lie still for 1-2 h, cold juice, feel FM – should have 6 movements in 2 h)

**PregHx**: Any complications (HTN, GDM, infections), IPS/FTS screening, last U/S (BPP score, growth/estimated fetal weight, position), last vaginal exam
**POBHx**: Every previous pregnancy and outcome: year, SVD/C-section/miscarriage/abortion, baby size, length of labour, use of vacuum or forceps, complications
**PMHx, Meds, Allergies, SHx**
**O/E**: Maternal vitals, fetal heart tracing (baseline, variability, presence of accelerations/decelerations), Leopold's, vaginal exam, U/S



**Reference Point for Describing Fetal Position**
- Occiput for cephalic presentation
- Sacrum for breech presentation
- Mentum for face presentation

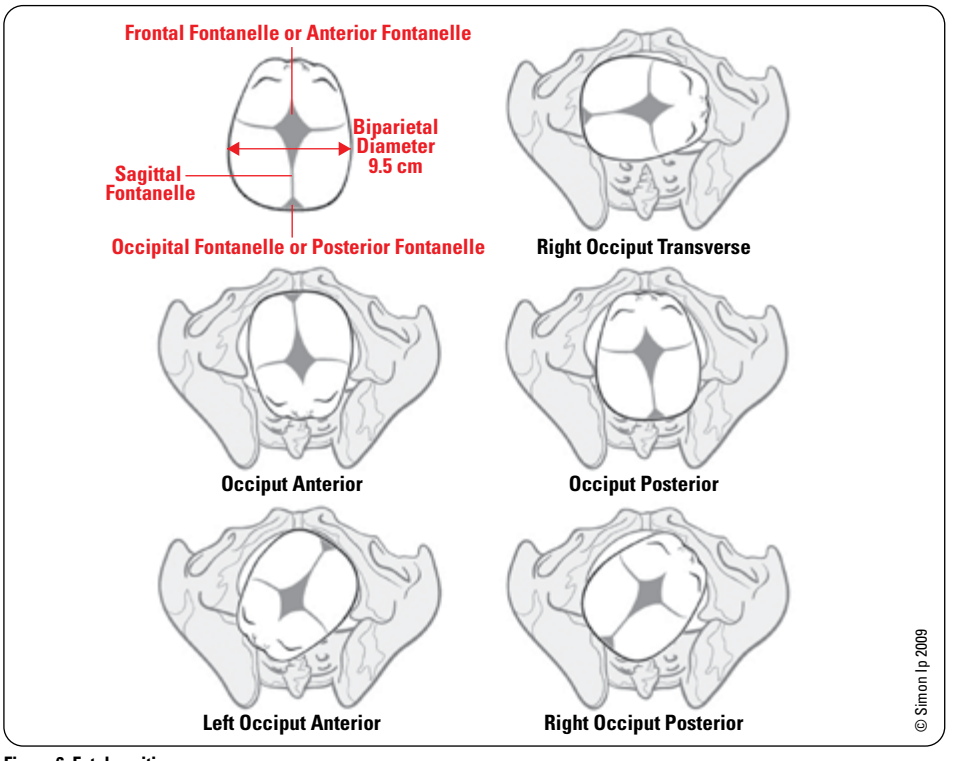



**Figure 6. Fetal positions**

# Four Stages of Labour

## First Stage of Labour (0 – 10 cm cervical dilation)

- latent phase
  - uterine contractions typically infrequent and irregular
  - slow cervical dilatation (usually to 4 cm) and effacement
- active phase
  - rapid cervical dilatation to full dilatation (nulliparous ≥1.0 cm/h, multiparous ≥1.2 cm/h)
  - phase of maximum slope on cervical dilatation curve
  - painful, regular contractions q2-3min, lasting 45-60 s
  - contractions strongest at fundus

## Second Stage of Labour (10 cm dilation – delivery of the baby)

- from full dilatation to delivery of the baby; duration varies based on parity, contraction quality, and type of analgesia
- mother feels a desire to bear down and push with each contraction
- women may choose a comfortable position that enhances pushing efforts and delivery
  - upright (semi-sitting, squatting) and LLDP are supported in the literature
- progress measured by descent

## Third Stage of Labour (delivery of the baby – delivery of the placenta)

- from baby's birth to separation and expulsion of the placenta
- can last up to 30 min before intervention is indicated
- demonstrated by gush of fresh blood, umbilical cord lengthening, uterine fundus changing shape (firm and globular), and rising upward
- active management: start oxytocin IV drip, or give 10 IU IM or 5 mg IV push, after delivery of anterior shoulder in anticipation of placental delivery, otherwise give after delivery of placenta
- routine oxytocin administration in third stage of labour can reduce the risk of PPH by >40%

## Fourth Stage of Labour

- first postpartum hour
- monitor vital signs and bleeding, repair lacerations
- ensure uterus is contracted (palpate uterus and monitor uterine bleeding)
- inspect placenta for completeness and umbilical cord for presence of 2 arteries and 1 vein
- 3rd and 4th stages of labour most dangerous to the mother (i.e. hemorrhage)

**Course of Normal Labour***

| Stage | Nulliparous | Multiparous |
|---|---|---|
| First | 6-18 h | 2-10 h |
| Second | 30 min-3 h | 5-30 min |
| Third | 5-30 min | 5-30 min |

*without epidural

**Signs of Placental Separation**

- Gush of blood
- Lengthening of cord
- Uterus becomes globular
- Fundus rises

**Continuous Support for Women During Childbirth**
Cochrane DB Syst Rev 2011;16:CD003766
**Study**: Systematic review of 21 RCTs from 11 countries, 15,061 women in labour.
**Intervention**: Continuous support during labour vs. usual care.
**Outcome**: Effects on mothers and their babies.
**Results**: Continuous intrapartum support increased likelihood of shorter labour, spontaneous vaginal birth, decrease in analgesia use, and a decrease in dissatisfaction with childbirth experience. Greatest benefit when provider is not a health care professional. Continuous support was also associated with decreased likelihood to have a Cesarean or instrumental vaginal birth, regional analgesia, or a baby with a low 5 min APGAR score.

# The Cardinal Movements of the Fetus During Delivery

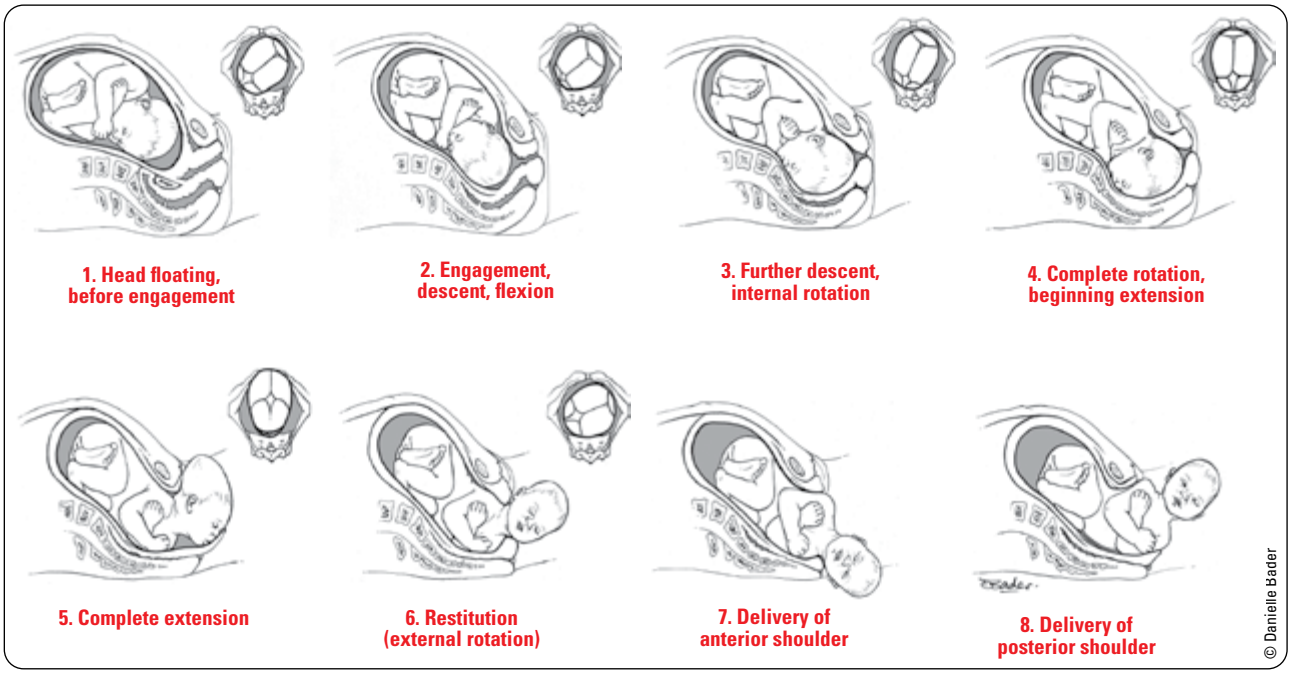



**Figure 7. Cardinal movements of fetus during delivery**
Adapted from illustration in Williams Obstetrics, 19th ed

# Analgesic and Anesthetic Techniques in Labour and Birth

- pain or anxiety leads to high endogenous catecholamines, which produce a direct inhibitory effect on uterine contractility

### Non-Pharmacologic Pain Relief Techniques

- reduction of painful stimuli
  - maternal movement, position change, counter-pressure, and abdominal compression
- activation of peripheral sensory receptors
  - superficial heat and cold
  - immersion in water during labour
  - touch and massage, acupuncture, and acupressure
  - TENS
  - intradermal injection of sterile water
  - aromatherapy
- enhancement of descending inhibitory pathways
  - attention focusing and distraction
  - hypnosis
  - music and audio analgesia
  - biofeedback

### Pharmacologic Methods (see Anesthesia and Perioperative Medicine, A27)

- nitrous oxide (e.g. self-administered Entonox®)
- narcotics (usually combined with anti-emetic)
- pudendal nerve block
- perineal infiltration with local anesthetic
- regional anesthesia (epidural block, combined spinal-epidural, and spinal)

# Fetal Monitoring in Labour




- see online **Fetal Heart Rate Tutorial**

### Vaginal Exam

- membrane status, as indicated by amniotic fluid (clear, pink, bloody, and meconium)
- cervical effacement (thinning), dilatation, consistency, position, and application
- fetal presenting part, position, and station
- bony pelvis size and shape
- monitor progress of labour at regular intervals and document in a partogram

## Intrapartum Fetal Monitoring

- intermittent fetal auscultation with Doppler device q15-30min for 1 min in first stage active phase following a contraction, q5min during second stage when pushing has begun
- continuous electronic FHR monitoring reserved for abnormal auscultation, prolonged labour, labour which is induced or augmented, meconium present, multiple gestation/fetal complication, and concerns about the fetus tolerating labour
  - use of continuous electronic monitoring shown to lead to higher intervention rates and no improvement in outcome for the neonate when used routinely in all patients (i.e. no risk factors)
  - techniques for continuous monitoring include external (Doppler) vs. internal (fetal scalp electrode) monitoring
- fetal scalp sampling should be used in conjunction with electronic FHR monitoring and contraction monitoring (CTG) to resolve the interpretation of abnormal or atypical patterns

## Electronic FHR Monitoring

- FHR measured by Doppler; contractions measured by tocometer
- described in terms of baseline FHR, variability (short-term, long-term), and periodicity (accelerations, decelerations)
- **Baseline FHR**
  - normal range is 110-160 bpm
  - parameter of fetal well-being vs. distress
- **Variability**
  - physiologic variability is a normal characteristic of FHR
  - variability is measured over a 15 min period and is described as: absent, minimal (<6 bpm), moderate (6-25 bpm), or marked (>25 bpm)
  - normal variability indicates fetal acid-base status is acceptable
  - can only be assessed by electronic contraction monitoring (CTG)
  - variability decreases intermittently even in healthy fetus
  - see Table 19, OB35
- **Periodicity**
  - accelerations: increase of ≥15 bpm for ≥15 s, (or ≥10 bpm for ≥10 s if <32 wk GA)
  - decelerations: 3 types, described in terms of shape, onset, depth, duration recovery, occurrence, and impact on baseline FHR and variability

**Table 17. Factors Affecting Fetal Heart Rate**

| | Fetal Tachycardia (FHR >160 bpm) | Fetal Bradycardia (FHR <110 bpm) | Decreased Variability |
|---|---|---|---|
| **Maternal Factors** | Fever, hyperthyroidism, anemia, dehydration | Hypothermia, hypotension, hypoglycemia, position, umbilical cord occlusion | Infection<br>Dehydration |
| **Fetal Factors** | Arrhythmia, anemia, infection, prolonged activity, chronic hypoxemia, congenital anomalies | Rapid descent, dysrhythmia, heart block, hyopoxia, vagal stimulation (head compression), hypothermia, acidosis | CNS anomalies<br>Dysrhythmia<br>Inactivity/sleep cycle, preterm fetus |
| **Drugs** | Sympathomimetics | β-blockers<br>Anesthetics | Narcotics, sedatives<br>Magnesium sulphate, β-blockers |
| **Uteroplacental** | Early hypoxia (abruption, HTN)<br>Chorioamnionitis | Late hypoxia (abruption, HTN)<br>Acute cord prolapse<br>Hypercontractility | Hypoxia |

**Approach to the Management of Abnormal FHR**

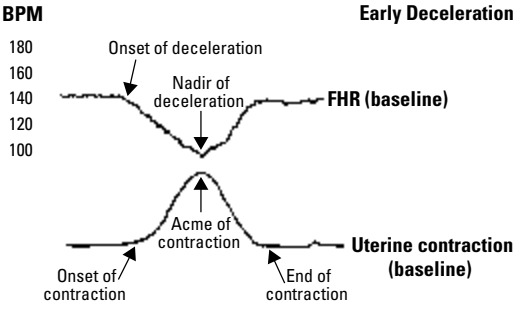
**POISON – ER**
**P**osition (LLDP)
**O**$_2$ (100% by mask)
**I**V fluids (corrects maternal hypotension)
Fetal **s**calp stimulation
Fetal **s**calp electrode
Fetal **s**calp pH
Stop **o**xytocin
**N**otify MD
Vaginal **e**xam to rule out cord prolapse
**R**ule out fever, dehydration, drug effects, prematurity
- If above fails, consider C/S

**Continuous CTG as a Form of EFM for Fetal Assessment During Labour**
Cochrane DB Syst Rev 2013;5:CD006066
**Purpose**: To examine the effectiveness of continuous electronic fetal monitoring or cardiotocography during labour.
**Selection Criteria**: Randomized and quasi-randomized controlled trials comparing continuous CTG (with and without fetal blood sampling) to a) no fetal monitoring, b) intermittent auscultation, or c) intermittent CTG.
**Results**: 13 trials, 37,000 women. Continuous CTG compared with intermittent auscultation showed no difference in overall perinatal death rate or cerebral palsy rates. Nonetheless, neonatal seizures were halved (RR 0.50, 95% CI 0.31-0.80) and there was a significant increase in C/S (RR 1.63, 95% CI 1.29-2.07) and instrumental vaginal birth (RR 1.15, 95% CI 1.01-1.33) with CTG.
**Conclusion**: Continuous CTG may reduce the incidence of neonatal seizures, but has no effect on cerebral palsy rates, infant mortality, or other measures of neonatal well-being. Continuous CTG was also associated with an increase in C/S and instrumental deliveries.

## Table 18. Comparison of Decelerations

### Early Decelerations

- Uniform shape with onset early in contraction, returns to baseline by end of contraction, mirrors contraction (nadir occurs at peak of contraction)
- Gradual deceleration and return to baseline
- Often repetitive; no effect on baseline FHR or variability
- Benign, due to vagal response to head compression

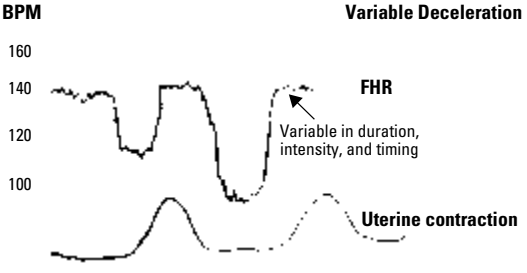



### Variable Decelerations

- Variable in shape, onset, and duration
- Most common type of periodicity seen during labour
- Often with abrupt drop in FHR >15 bpm below baseline (>15 s, <2 min); usually no effect on baseline FHR or variability
- Due to cord compression or, in second stage, forceful pushing with contractions

### Complicated Variable Decelerations

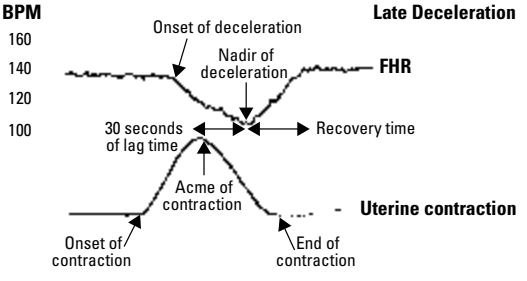
- FHR drop <70 bpm for >60 s
- Loss of variability or decrease in baseline after deceleration
- Biphasic deceleration
- Slow return to baseline
- Baseline tachycardia or bradycardia
- May be associated with fetal acidemia




**Rule of 60s Suggesting Severe Variable Decelerations**
Deceleration to <60 bpm
>60 bpm below baseline
>60 s in duration with slow return to baseline

### Late Decelerations

- Uniform shape with onset, nadir, and recovery occurring after peak of contraction, slow return to baseline
- May cause decreased variability and change in baseline FHR
- Due to fetal hypoxia and acidemia, maternal hypotension, or uterine hypertonus
- Usually a sign of uteroplacental insufficiency (an ominous sign)




## Table 19. Classification of Intrapartum EFM Tracings

| | Normal Tracing (Category 1) | Atypical Tracing* (Category 2) | Abnormal Tracing* (Category 3) |
|---|---|---|---|
| **Baseline** | 110-160 bpm | Bradycardia 100-110 bpm<br>Tachycardia >160 for 30-80 min<br>Rising baseline | Bradycardia <100 bpm<br>Tachycardia >160 bpm for >80 min<br>Erratic baseline |
| **Variability** | 6-25 bpm<br>≤5 bpm for <40 min | ≤5 bpm for 40-80 min | <5 bpm for >80 min<br>≥25 bpm for >10 min |
| **Decelerations** | None<br>Early decelerations<br>Occasional uncomplicated variable decelerations | Repetitive (≥3) uncomplicated variable decelerations<br>Occasional late decelerations<br>Any prolonged deceleration (2-3 min) | Repetitive (≥3) complicated variable decelerations<br>Repetitive late decelerations<br>Any prolonged deceleration (≥3 min) |
| **Accelerations** | Accelerations spontaneous or during scalp stimulation | Absent with scalp stimulation | Nearly absent |
| **Action** | EFM may be interrupted for ≤30 min if mother/fetus stable | Further assessment required | Action required: review clinical situation, obtain scalp pH, prepare for possible delivery |

Adapted from SOGC Guidelines, September 2008
*Previous classification was "reassuring" vs. "non-reassuring", but distinction is now made between tracings that have some concerning changes but do not require immediate action (atypical) versus those with major concerns requiring immediate intervention (abnormal)

## Fetal Scalp Blood Sampling

- cervix must be adequately dilated
- indicated when atypical or abnormal fetal heart rate is suggested by clinical parameters including heavy meconium or moderately to severely abnormal FHR patterns (including unexplained low variability, repetitive late decelerations, complex variable decelerations, and fetal cardiac arrhythmias)

- done by measuring pH or more recently fetal lactate
  - pH ≥7.25, lactate <4.2 mmol/L: normal, repeat if abnormal FHR persists
  - pH 7.21-7.24, lactate 4.2-4.8 mmol/L: repeat assessment in 30 min or consider delivery if rapid fall since last sample
  - pH ≤7.20, lactate >4.8 mmol/L indicates fetal acidosis, delivery is indicated
- contraindications
  - known or suspected fetal blood dyscrasia (hemophilia, vWD)
  - active maternal infection (HIV, genital herpes)

### Fetal Oxygenation

- uterine contractions during labour decrease uteroplacental blood flow, which results in reduced oxygen delivery to the fetus
- most fetuses tolerate this reduction in flow and have no adverse effects
- distribution of oxygen to the fetus depends on maternal, uteroplacental, and fetal factors
- fetal response to hypoxia/asphyxia:
  - decreased movement, tone, and breathing activities
  - anaerobic metabolism (decreased pH)
  - transient fetal bradycardia followed by fetal tachycardia
  - redistribution of fetal blood flow
- increased flow to brain, heart, and adrenals
- decreased flow to kidneys, lungs, gut, liver, and peripheral tissues
- increase in blood pressure

**Table 20. Factors Affecting Fetal Oxygenation**

| Factor | Mechanism | Example |
|---|---|---|
| **Maternal** | Decreased maternal oxygen carrying capacity | Significant anemia (iron deficiency, hemoglobinopathies), carboxyhemoglobin (smokers) |
| | Decreased uterine blood flow | Hypotension (blood loss, sepsis), regional anesthesia, maternal positioning |
| | Chronic maternal conditions | Vasculopathies (SLE, type 1 DM, chronic HTN), APS, cyanotic heart disease, COPD |
| **Uteroplacental** | Uterine hypertonus | Placental abruption, hyperstimulation secondary to oxytocin, prostaglandins, or normal labour |
| | Uteroplacental dysfunction | Placental abruption, placental infarction (dysfunction marked by IUGR, oligohydramnios, abnormal Doppler studies), chorioamnionitis, placental edema (DM, hydrops), placental senescence (post-dates) |
| **Fetal** | Cord compression | Oligohydramnios, cord prolapse, or entanglement |
| | Decreased fetal oxygen carrying capacity | Significant anemia (isoimmunization, feto-maternal bleed), carboxyhemoglobin (exposure to smokers) |

# Induction of Labour

### Definition

- artificial initiation of labour in a pregnant woman prior to spontaneous initiation to deliver the fetus and placenta

### Prerequisites for Labour Induction

- capability for C/S if necessary
- maternal
  - inducible/ripe cervix: short, thin, soft, anterior cervix with open os
  - if cervix is not ripe, use prostaglandin vaginal insert (Cervidil®), prostaglandin gel (Prepidil®), misoprostol (Cytotec®), or Foley catheter
- fetal
  - normal fetal heart tracing
  - cephalic presentation
  - adequate fetal monitoring available
- likelihood of success determined by Bishop score
  - cervix considered unfavourable if <6
  - cervix favourable if ≥6
  - score of 9-13 associated with high likelihood of vaginal delivery



Induction is indicated when the risk of continuing pregnancy exceeds the risks associated with induced labour and delivery

**Table 21. Bishop Score**

| Cervical Characteristic | 0 | 1 | 2 | 3 |
|---|---|---|---|---|
| **Position** | Posterior | Mid | Anterior | – |
| **Consistency** | Firm | Medium | Soft | – |
| **Effacement (%)** | 0-30 | 40-50 | 60-70 | ≥80 |
| **Dilatation (cm)** | 0 | 1-2 | 3-4 | ≥5 |
| **Station of Fetal Head** | -3 | -2 | -1, 0 | +1, +2, +3 |

**Induction vs. Augmentation**
**Induction** is the artificial initiation of labour
**Augmentation** promotes contractions when spontaneous contractions are inadequate

### Indications
- post-dates pregnancy (generally >41 wk) = most common reason for induction
- maternal factors
  - DM = second most common reason for induction
  - gestational HTN ≥37 wk
  - preeclampsia
  - other maternal medical problems, e.g. renal or lung disease, chronic hypertension, and cholestasis
  - maternal age over 40
- maternal-fetal factors
  - isoimmunization, PROM, chorioamnionitis
- fetal factors
  - suspected fetal jeopardy as evidenced by biochemical or biophysical indications
  - macrosomia, fetal demise, IUGR, oligo/polyhydramnios, anomalies requiring surgical intervention, and twins
  - previous stillbirth or low PAPP-A

**Consider the Following Before Induction**
- Indication for induction
- Contraindications
- GA
- Cervical favourability
- Fetal presentation
- Potential for CPD
- Fetal well-being/FHR
- Membrane status

### Risks
- failure to achieve labour and/or vaginal birth
- uterine hyperstimulation with fetal compromise or uterine rupture
- maternal side effects to medications
- uterine atony and PPH

### Contraindications
- maternal
  - prior classical or inverted T-incision C/S or uterine surgery (e.g. myomectomy)
  - unstable maternal condition
  - active maternal genital herpes
  - invasive cervical carcinoma
  - pelvic structure deformities
- maternal-fetal
  - placenta previa or vasa previa
  - cord presentation
- fetal
  - fetal distress, malpresentation/abnormal lie, or preterm fetus without lung maturity

## Induction Methods

### CERVICAL RIPENING

### Definition
- use of medications or other means to soften, efface, and dilate the cervix; increases likelihood of successful induction
- ripening of an unfavourable cervix (Bishop score <6) is warranted prior to induction of labour

### Methods
- intravaginal prostaglandin PGE2 gel (Prostin® gel): long and closed cervix
  - recommended dosing interval of prostaglandin gel is every 6-12 h up to 3 doses
- intravaginal PGE2 (Cervidil®): long and closed cervix, may use if ROM
  - continuous release, can be removed if needed
  - controlled release PGE2
- intracervical PGE2 (Prepidil®)
- intravaginal PGE1 misoprostol (Cytotec®): long and closed cervix
  - inexpensive, stored at room temperature
  - more effective than PGE2 for achieving vaginal delivery and less epidural use
- Foley catheter placement to mechanically dilate the cervix

**Evidence for Cervical Ripening Methods (SOGC Guidelines)**
- Meta-analysis of five trials has concluded that the use of oxytocin to ripen the cervix is not effective
- Since the best dose and route of misoprostol for labour induction with a live fetus are not known and there are concerns regarding hyperstimulation, the use of misoprostol for induction of labour should be within clinical trials only (Level Ib evidence) or in cases of intrauterine fetal death to initiate labour

**Intravaginal PGE2 (Cervidil®) Compared to Intravaginal Prostaglandin Gel**
4 RCTs have compared the two with varying results, depending on the dosing regime of gel used.
Theoretical advantages of Cervidil®:
- Slow, continuous release
- Only one dose required
- Ability to use oxytocin 30 min after removal vs. 6 hours for gel
- Ability to remove insert if required (i.e. excessive uterine activity)

## INDUCTION OF LABOUR

### Amniotomy

- artificial ROM (amniotomy) to stimulate prostaglandin synthesis and secretion; may try this as initial measure if cervix is open and soft, the membranes can be felt, and if the head is present at the cervix
- few studies address the value of amniotomy alone for induction of labour
- amniotomy plus intravenous oxytocin: more women delivered vaginally at 24 h than amniotomy alone (relative risk = 0.03) and had fewer instrumental vaginal deliveries (relative risk = 5.5)

### Oxytocin

- oxytocin (Pitocin®): 10 U in 1L NS, run at 0.5-2 mU/min IV increasing by 1-2 mU/min q20-60min
- reduces rate of unsuccessful vaginal deliveries within 24 h when used alone (8.3% vs. 54%, RR 0.16)
- ideal dosing regimen of oxytocin is not known
- current recommendations: use the minimum dose to achieve active labour and increase q30min as needed
- reassessment should occur once a dose of 20 mU/min is reached
- potential complications
  - hyperstimulation/tetanic contraction (may cause fetal distress or uterine rupture)
  - uterine muscle fatigue, uterine atony (may result in PPH)
  - vasopressin-like action causing anti-diuresis



Oxytocin t1/2 = 3-5 min

# Augmentation of Labour

- augmentation of labour with oxytocin is used to promote adequate contractions when spontaneous contractions are inadequate and cervical dilatation or descent of fetus fails to occur



Provided there are no contraindications, oxytocin is utilized to improve uterine contraction strength and/or frequency

# Abnormalities and Complications of Labour and Delivery

## Abnormal Progression of Labour (Dystocia)

### Definition

- expected patterns of descent of the presenting part and cervical dilatation fail to occur in the appropriate time frame; can occur in all stages of labour
- during active phase: >4 h of <0.5 cm/h
- during 2nd stage: >1 h with no descent during active pushing

### Etiology

- Power (leading cause): contractions (hypotonic, uncoordinated), inadequate maternal expulsive efforts
- Passenger: fetal position, attitude, size, anomalies (hydrocephalus)
- Passage: pelvic structure (CPD), maternal soft tissue factors (tumours, full bladder or rectum, vaginal septum)
- Psyche: hormones released in response to stress may contribute to dystocia; psychological and physiological stress should be evaluated as part of the management once dystocia has been diagnosed



**The 4 Ps of Dystocia**
**P**ower
**P**assenger
**P**assage
**P**syche

### Management

- confirm diagnosis of labour (rule out false labour)
- search for factors of CPD
- concern for dystocia if adequate contractions measured by intrauterine pressure catheter (IUPC) with no descent/dilatation for >2 h
- management: if CPD ruled out, IV oxytocin augmentation ± amniotomy

### Risks of Dystocia

- inadequate progression of labour is associated with an increased incidence of:
  - maternal stress
  - maternal infection
  - PPH
  - need for neonatal resuscitation
  - fetal compromise (from uterine hyperstimulation)
  - uterine rupture
  - hypotension

# Shoulder Dystocia

### Definition
- fetal anterior shoulder impacted above pubic symphysis after fetal head has been delivered
- life threatening emergency

### Etiology/Epidemiology
- incidence 0.15-1.4% of deliveries
- occurs when breadth of shoulders is greater than biparietal diameter of the head

### Risk Factors
- maternal: obesity, DM, multiparity, and previous shoulder dystocia
- fetal: prolonged gestation or macrosomia (especially if associated with GDM)
- labour
  - prolonged 2nd stage
  - instrumental midpelvic delivery

### Presentation
- "turtle sign": head delivered but retracts against inferior portion of pubic symphysis
- complications
  - fetal
    - hypoxic ischemic encephalopathy (chest compression by vagina or cord compression by pelvis can lead to hypoxia)
    - brachial plexus injury (Erb's palsy: C5-C7; Klumpke's palsy: C8-T1), 90% resolve within 6 mo
    - fracture (clavicle, humerus, and cervical spine)
    - death
  - maternal
    - perineal injury
    - PPH (uterine atony or lacerations)
    - uterine rupture

### Treatment
- goal: to displace anterior shoulder from behind symphysis pubis; follow a stepwise approach of maneuvers until goal achieved (see sidebar)
- other options
  - cleidotomy (deliberate fracture of neonatal clavicle)
  - Zavanelli maneuver: replacement of fetus into uterine cavity and emergent C/S
  - symphysiotomy

### Prognosis
- 1% risk of long-term disability for infant

**Approach to the Management of Shoulder Dystocia**

**ALARMER**
**A**pply suprapubic pressure and ask for help
**L**egs in full flexion (McRobert's maneuver)
**A**nterior shoulder disimpaction (suprapubic pressure)
**R**elease posterior shoulder by rotating it anteriorly with hand in the vagina under adequate anesthesia
**M**anual corkscrew i.e. rotate the fetus by the posterior shoulder until the anterior shoulder emerges from behind the maternal symphysis
**E**pisiotomy
**R**ollover (on hands and knees)
*Note that suprapubic pressure and McRobert's maneuver together will resolve 90% of cases

# Umbilical Cord Prolapse

### Definition
- descent of the cord to a level adjacent to or below the presenting part, causing cord compression between presenting part and pelvis

### Etiology/Epidemiology
- increased incidence with prematurity/PROM, fetal malpresentation (~50% of cases), low-lying placenta, polyhydramnios, multiple gestation, and CPD
- incidence: 1/200-1/400 deliveries

### Presentation
- visible or palpable cord
- FHR changes (variable decelerations, bradycardia, or both)

### Treatment
- emergency C/S if not fully dilated and vaginal delivery not imminent
- $O_2$ to mother, monitor fetal heart
- alleviate pressure of the presenting part on the cord by elevating fetal head with a pelvic exam (maintain this position until C/S)
- keep cord warm and moist by replacing it into the vagina ± applying warm saline soaks
- roll mother onto all fours or position mother in Trendelenburg or knee-to-chest position
- if fetal demise or too premature (<22 wk), allow labour and delivery

**Umbilical Cord Accident Causes**
- Nuchal cord
  - Type A (looped)
  - Type B (hitched)
- Body loop
- Single artery
- True knot
- Torsion
- Velamentous
- Short cord <35 cm
- Long cord >80 cm

- 1/3 of protraction disorders develop into 2° arrest of dilatation due to CPD
- 2/3 of protraction disorders progress through labour to vaginal delivery

# Uterine Rupture

### Definition
- associated with previous uterine scar (in 40% of cases), hyperstimulation with oxytocin, grand multiparity, and previous intrauterine manipulation
- generally occurs during labour, but can occur earlier with a classical incision
- 0.5-0.8% incidence, up to 12% with classical incision

### Presentation
- prolonged fetal bradycardia – most common presentation
- acute onset of constant lower abdominal pain, may not have pain if receiving epidural analgesia
- hyper/hypotonic uterine contractions
- abnormal progress in labour
- vaginal bleeding
- intra-abdominal hemorrhage
- loss of station of the presenting fetal part
- maternal tachycardia, hypotension, or shock

### Risk Factors
- uterine scarring (i.e. previous uterine surgeries including C/S (especially classical incision), perforation with D&C, and myomectomy)
- excessive uterine stimulation (i.e. protracted labour, oxytocin, prostaglandins)
- uterine trauma (i.e. operative equipment, ECV)
- multiparity
- uterine abnormalities
- malpresentation
- placenta accreta

### Treatment
- rule out placental abruption
- maternal stabilization (may require hysterectomy), treat hypovolemia
- immediate delivery for fetal survival

### Complications
- maternal mortality 1-10%
- maternal hemorrhage, shock, DIC
- amniotic fluid embolus
- hysterectomy if uncontrollable hemorrhage
- fetal distress, associated with infant mortality as high as 15%

**Maternal Mortality Causes**
- Thromboembolism
- Cardiac event
- Suicide
- Sepsis
- Ectopic pregnancy
- HTN
- Amniotic fluid embolism
- Hemorrhage

* In Canada (2013), lifetime risk of maternal death is 1 in 5200

# Amniotic Fluid Embolus

### Definition
- amniotic fluid debris in maternal circulation triggering an anaphylactoid immunologic response

### Etiology/Epidemiology
- rare intrapartum or immediate postpartum complication
- 13-30% maternal mortality rate
- leading cause of maternal death in induced abortions and miscarriages
- 1/8000-1/80,000 births

### Risk Factors
- placental abruption
- rapid labour
- multiparity
- uterine rupture
- uterine manipulation
- induction medication and procedures

### Differential Diagnosis
- pulmonary embolus, drug-induced anaphylaxis, septic shock, eclampsia, HELLP syndrome, abruption, and chronic coagulopathy

### Presentation
- sudden onset of respiratory distress, cardiovascular collapse (hypotension, hypoxia), and coagulopathy
- seizure in 10%
- ARDS and left ventricular dysfunction seen in survivors

### Management
- should be managed in the ICU by a multidisciplinary team
- supportive measures (high flow $O_2$, ventilation support, fluid resuscitation, inotropic support, ± intubation) and coagulopathy correction

## Chorioamnionitis

### Definition
- infection of the chorion, amnion, and amniotic fluid

### Etiology/Epidemiology
- incidence 1-5% of term pregnancies and up to 25% in preterm deliveries
- ascending infection (microorganisms from vagina)
- predominant microorganisms include: GBS, *Bacteroides* and *Prevotella* species, *E. coli*, and anaerobic *Streptococcus*



**Clinical Features of Chorioamnionitis**
- Temperature
- Tachycardia (maternal or fetal)
- Tenderness (uterine)
- Foul discharge

### Risk Factors
- low parity, prolonged ROM, long labour, multiple vaginal exams during labour, and internal monitoring
- bacterial vaginosis and other vaginal infections

### Clinical Features
- maternal fever ≥38° C, maternal or fetal tachycardia, uterine tenderness, and foul and purulent cervical discharge

### Investigations
- CBC: leukocytosis
- amniotic fluid: Gram stain, glucose, or culture results consistent with infection

### Treatment
- IV antibiotics
  - ampicillin 2 g IV q6h + gentamicin 2 mg/kg load, then 1.5 mg/kg IV q8h
  - anaerobic coverage (i.e. clindamycin 900 mg IV q8h)
  - if at risk for endometritis, continue treatment post-partum especially if C/S delivery
- antipyretics
- proper labour progression (not an indication for immediate delivery or C/S)

### Complications
- bacteremia of mother or fetus, wound infection if C/S, pelvic abscess, neonatal meningitis, neonatal sepsis, and neonatal death
- long-term infant complications: cerebral palsy and bronchopulmonary dysplasia

## Meconium

### Epidemiology
- present early in labour in 10% of pregnancies, more common in postdate pregnancies
- in general, meconium may be present in up to 25% of all labours; usually NOT associated with poor outcome
- concern if fluid changes from clear to meconium-stained
- always abnormal if seen in preterm fetus



Particulate (thickened) meconium is associated with lower APGARs, an increased risk of meconium aspiration, and perinatal death. Particulate meconium generally has a darker green or black colour, whereas thin meconium is usually yellow to light green

### Etiology
- likely cord compression ± uterine hypertonia
- may indicate undiagnosed breech
- increasing meconium during labour may be a sign of fetal distress

### Features
- may be watery or thicker (particulate)
- light yellow/green or dark green-black in colour

### Treatment
- call respiratory therapy, neonatology, or pediatrics to delivery room
- closely monitor FHR for signs of fetal distress

# Operative Obstetrics

## Operative Vaginal Delivery

### Definition
- forceps or vacuum extraction

### Indications
- fetal
  - atypical or abnormal fetal heart rate tracing, evidence of fetal compromise
  - consider if second stage is prolonged, as this may be due to poor contractions or failure of fetal head to rotate
- maternal
  - need to avoid voluntary expulsive effort (e.g. cardiac/cerebrovascular disease)
  - exhaustion, lack of cooperation, and excessive analgesia may impair pushing effort

### Contraindications
- unknown fetal head presentation
- unengaged head
- fetal bone demineralization disorder (e.g. osteogenesis imperfecta)
- fetal bleeding disorder (e.g. hemophilia or vWD)

**Prerequisites for Operative Vaginal Delivery**

**ABCDEFGHIJK**
**A**nesthesia (adequate)
**B**ladder empty
**C**ervix fully dilated and effaced with ROM
**D**etermine position of fetal head
**E**quipment ready (including facilities for emergent C/S)
**F**ontanelle (posterior fontanelle midway between thighs)
**G**entle traction
**H**andle elevated
**I**ncision (episiotomy)
Once **j**aw visible remove forceps
**K**nowledgeable operator

## Forceps

### Outlet Forceps Position
- head visible between labia in between contractions
- sagittal suture in or close to AP diameter
- rotation cannot exceed 45°

### Low Forceps Position
- presenting part at station +2 or greater
- subdivided based on whether rotation less than or greater than 45°

### Mid Forceps Position
- presenting part below spines but above station +2

### Types of Forceps
- Simpson or Tucker-McLane forceps for OA presentations
- Kielland (rotational) forceps when rotation of head or correction of asynclitism is required
- Piper forceps for after-coming head in breech delivery
- Wrigley's for preterm babies

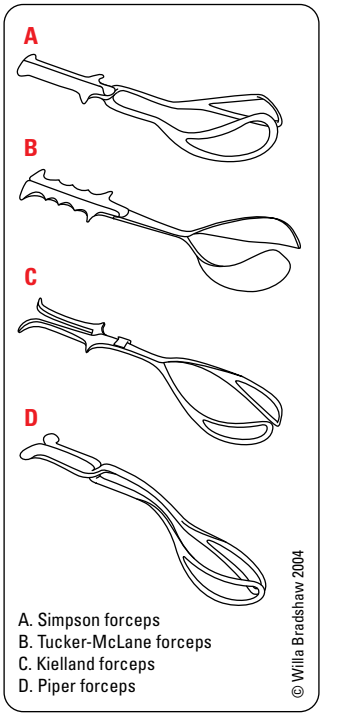



**Figure 8. Types of forceps**

## Vacuum Extraction

- traction instrument used as alternative to forceps delivery; aids maternal pushing
- contraindications: <34 wk GA (<2500 g), fetal head deflexed, fetus requires rotation, fetal condition (e.g. bleeding disorder)

**Limits for Trial of Vacuum**
- After 3 pulls over 3 contractions with no progress
- After 3 pop-offs with no obvious cause
- 20 min and delivery is not imminent

**Table 22. Advantages and Disadvantages of Forceps vs. Vacuum Extraction**

| | Forceps | Vacuum Extraction |
|---|---|---|
| **Advantages** | Higher overall success rate for vaginal delivery<br>Decreased incidence of fetal morbidity | Easier to apply<br>Less anesthesia required<br>Less maternal soft-tissue injury compared to forceps |
| **Disadvantages** | Greater incidence of maternal injury | Suitable only for vertex presentations<br>Maternal pushing required<br>Contraindicated in preterm delivery |
| **Complications** | Maternal: anesthesia risk, lacerations, injury to bladder, uterus, or bone, pelvic nerve damage, PPH, and infections<br>Fetal: fractures, facial nerve palsy, trauma to face/scalp, intracerebral hemorrhage, cephalohematoma, and cord compression | Increased incidence of cephalohematoma and retinal hemorrhages, and jaundice compared to forceps<br>Subgaleal hemorrhage<br>Subaponeurotic hemorrhage<br>Soft tissue trauma |

# Lacerations

- first degree: involves skin and vaginal mucosa but not underlying fascia and muscle
- second degree: involves fascia and muscles of the perineal body but not the anal sphincter
- third degree: involves the anal sphincter (partial IIIa or complete IIIb)
- fourth degree: extends through the anal sphincter into the rectal mucosa
- for third and fourth degree tears, a single prophylactic dose of IV antibiotics (2nd generation cephalosporin, e.g. cefoxitin or cefotetan) should be administered to reduce perineal wound complications; laxatives should also be prescribed and constipation should be avoided

# Episiotomy

## Definition

- incision in the perineal body at the time of delivery
- essentially a controlled second degree laceration
- midline: incision through central tendinous portion of perineal body and insertions of superficial transverse perineal and bulbocavernosus muscles
  - heals better, but increases risk of 3rd/4th degree tears
- mediolateral: incision through bulbocavernosus, superficial transverse perineal muscle, and levator ani
  - reduced risk of extensive tear but more painful

## Indications

- to relieve obstruction of the unyielding perineum
- to expedite delivery (e.g. abnormal FHR pattern)
- instrumental delivery
- controversial between practitioners as to whether it is preferable to make a cut or let the perineum tear as needed
- current evidence suggests letting perineum tear and then repair as needed (restricted use)

## Complications

- infection, hematoma, extension into anal musculature or rectal mucosa, fistula formation, and incontinence

**Risk Factors for the Development of Obstetric Anal Sphincter Injuries in Modern Obstetric Practice**
Obstet Gynecol 2018;131(2):290-96
**Objective**: To characterize the rate of obstetric anal sphincter injuries and identify key risk factors of obstetric anal sphincter injuries, including duration of the second stage of labour.
**Methods**: Retrospective cohort study including all singleton, term, cephalic vaginal deliveries from 2013 to 2014.
**Results**: The overall incidence rate of obstetric anal sphincter injuries was 4.9% (3.6% of women who delivered spontaneously vs 24.0% of women who had a vacuum-assisted vaginal delivery, P<.001, CI 18.1–22.6%). In bivariate and multivariate analyses, obstetric anal sphincter injury incidence was higher among women with second stage of labour longer than 2 hours, Asian race, nulliparity, vaginal birth after cesarean delivery, episiotomy, and vacuum delivery. Women with a vacuum-assisted vaginal delivery had four times the odds of obstetric anal sphincter injury (adjusted odds ratio [OR] 4.23, 95% CI 3.59-4.98) and those whose second stage of labour lasted at least 180 minutes vs less than 60 minutes had three times the odds of incurring obstetric anal sphincter injury (adjusted OR 3.20, 95% CI 2.62-3.89).

# Cesarean Delivery

## Epidemiology

- overall 28% rate in Canada (range 18.5-35.3% by province/territory)

## Indications

- maternal: obstruction, active herpetic lesion on vulva, invasive cervical cancer, previous uterine surgery (past C/S is most common), and underlying maternal illness (eclampsia, HELLP syndrome, heart disease)
- maternal-fetal: failure to progress, placental abruption or previa, and vasa previa
- fetal: abnormal fetal heart tracing, malpresentation, cord prolapse, and certain congenital anomalies

## Types of Cesarean Incisions

- skin
  - transverse (Pfannenstiel)
  - decreased exposure and slower entry
  - improved strength and cosmesis
  - vertical midline
  - rapid peritoneal entry and increased exposure
  - increased dehiscence
- uterine
  - low transverse (most common): in non-contractile lower segment
- decreased chance for rupture in subsequent pregnancies
  - low vertical
  - used for very preterm infants or poorly developed maternal lower uterine segment
  - classical (rare): in thick, contractile segment
  - used for transverse lie, preterm breech, fetal anomaly, >2 fetuses, lower segment adhesions, obstructing fibroid, and inaccessible lower uterine segment (e.g. morbid obesity)

## Risks/Complications

- anaesthetic complications (e.g. aspiration)
- hemorrhage (average blood loss ~1000 cc)
- infection (UTI, wound, and endometritis)
  - single dose prophylactic antibiotic should be used (e.g. cefazolin 1-2 g)
- injury to surrounding structures (bowel, bladder, ureter, and uterus)
- thromboembolism (DVT, PE)
- increased recovery time/hospital stay
- maternal mortality (<0.1%)

**Common OR Questions**

**7 Layers to Dissect**
Skin, fatty layer, fascia, muscle separation (rectus abdominis), peritoneum, bladder flap, uterus

**Layers of the Rectus Sheath**
Above the arcuate line: external oblique, external internal oblique, internal oblique, rectus abdominis, internal internal oblique, transversus abdominis
Below the arcuate line: external oblique, internal oblique, transversus abdominis, rectus abdominis

**Name of the Obliterated Umbilical Ligament** Urachus

Most C/S performed with regional analgesia

# Trial of Labour after Cesarean Section (TOLAC)

- should be recommended if no contraindications after previous low transverse incision
- success rate varies with indication for previous C/S (generally 60-80%)
- risk of uterine rupture (<1% with low transverse incision), increased by interval <18 mo and one layer closure

Contraindications
- previous classical, inverted T, or unknown uterine incision, or complete transection of uterus (6% risk of rupture)
- history of uterine surgery (e.g. myomectomy) or previous uterine rupture
- multiple gestation
- non-vertex presentation or placenta previa
- inadequate facilities or personnel for emergency C/S

**VBAC***
- Rate of successful VBAC ranges from 60-82%
- No significant difference in maternal deaths or hysterectomies between VBAC or C/S
- Uterine rupture more common in VBAC group
- Evidence regarding fetal outcome is lacking

*Safety of vaginal birth after Cesarean section: A systematic review. *Obstet Gynecol* 2004;103:420-9

# Puerperal Complications

- puerperium: 6 wk period of adjustment after pregnancy when pregnancy-induced anatomic and physiologic changes are reversed

# Postpartum Hemorrhage

## Definition
- loss of >1000 ml of blood or bleeding associated with signs/symptoms of hypovolemia within 24 hours of birthing process regardless of mode of delivery
- primary – within first 24 h postpartum
- secondary – after 24 h but within first 12 wk

## Epidemiology
- incidence 5-15%

## Etiology (4 Ts)
**1. Tone (uterine atony)**
- most common cause of PPH (70-80%)
- avoid with active management of 3rd stage of labour with 1) oxytocin administration 2) uterine massage 3) umbilical cord traction
- due to:
  - overdistended uterus (polyhydramnios, multiple gestations, and macrosomia)
  - uterine muscle exhaustion (prolonged or rapid labour, grand multiparity, oxytocin use, and general anesthetic)
  - uterine distortion (fibroids)
  - intra-amniotic infection (fever or prolonged ROM)
  - bladder distension (preventing uterine contraction)

**2. Tissue**
- retained placental products (membranes, cotyledon, or succenturiate lobe)
- retained blood clots in an atonic uterus
- gestational trophoblastic neoplasia
- abnormal placentation (e.g. placenta previa or placental abruption)

**3. Trauma**
- laceration (vagina, cervix, or uterus), episiotomy, hematoma (vaginal, vulvar, or retroperitoneal), uterine rupture, and uterine inversion

**4. Thrombin**
- coagulopathy (pre-existing or acquired)
  - most identified prior to delivery (low platelets increases risk)
  - includes hemophilia, DIC, ITP, TTP, and vWD (most common)
  - therapeutic anti-coagulation

Uterine atony is the most common cause of PPH

**DDx of Early PPH – 4 Ts**
**T**one (atony)
**T**issue (retained placenta, clots)
**T**rauma (laceration, inversion)
**T**hrombin (coagulopathy)

**DDx of Late PPH**
Retained products
± endometritis
Sub-involution of uterus

## Investigations
- assess degree of blood loss and shock by clinical exam
- explore uterus and lower genital tract for evidence of atony, retained tissue, or trauma
- may be helpful to observe red-topped tube of blood – no clot in 7-10 min indicates coagulation problem

## Management
- ABCs, call for help
- 2 large bore IVs, run crystalloids wide open
- CBC, coagulation profile, cross and type pRBCs
- treat underlying cause
- Foley catheter to empty bladder and monitor urine output

### Medical Therapy
- oxytocin 10 IU IM is preferred in low-risk vaginal deliveries, oxytocin IV infusion (20-40 IU in 1000 mL crystalloid at 150 mL/h) is an acceptable alternative. Oxytocin 5-10 IU IV bolus (20-40 IU in 250 mL crystalloid) can be used after vaginal birth, but not with elective C/S
- carbetocin, a long-acting oxytocin, 100 μg IV bolus over 1 min for elective C/S or 100 ug IM for vaginal deliveries with 1 risk factor for PPH (instead of a continuous oxytocin infusion)
- methylergonavine maleate (ergotamine) 0.25 mg IM/IMM q15min up to 1.25 mg; can be given as IV bolus of 0.125 mg (may exacerbate HTN)
- carboprost (Hemabate®), a synthetic PGF-1α analog, 250 μg IM/IMM q15min to max 2 mg (major prostaglandin side effects and contraindicated in cardiovascular, pulmonary, renal, and hepatic dysfunction)
- misoprostol 600-800 μg PO/SL (faster) or PR/PV (side effect: pyrexia if >600 μg)
- tranexamic acid (Cyklokapron®), an antifibrinolytic, 1 g IV

### Local Control
- bimanual massage: elevate the uterus and massage through patient's abdomen
- uterine packing (mesh with antibiotic treatment)
- Bakri Balloon for tamponade: may slow hemorrhage enough to allow time for correction of coagulopathy or for preparation of an OR

### Surgical Therapy (Intractable PPH)
- D&C (beware of vigorous scraping, which can lead to Asherman's syndrome)
- embolization of uterine artery or internal iliac artery by interventional radiologist
- laparotomy with bilateral ligation of uterine artery (may be effective), ovarian artery, or hypogastric artery, compression sutures (B-Lynch or Cho sutures)
- hysterectomy last option, with angiographic embolization if post-hysterectomy bleeding

## Retained Placenta

### Definition
- placenta undelivered after 30 min postpartum

### Etiology
- placenta separated but not delivered
- abnormal placental implantation (placenta accreta, placenta increta, and placenta percreta)

### Risk Factors
- placenta previa, prior C/S, post-pregnancy curettage, prior manual placental removal, and uterine infection

### Clinical Features
- risk of PPH and infection

### Investigations
- explore uterus
- assess degree of blood loss

### Management
- 2 large bore IVs, type and screen
- Brandt maneuver (firm traction on umbilical cord with one hand applying suprapubic pressure cephalad to avoid uterine inversion by holding uterus in place)
- oxytocin 10 IU in 20 mL NS into umbilical vein
- manual removal if above fails
- D&C if required (U/S guidance if available)
- cefazolin 2 g IV if manual removal or D&C

## Uterine Inversion



### Definition
- inversion of the uterus through cervix ± vaginal introitus

### Etiology/Epidemiology
- often iatrogenic (excess cord traction with fundal placenta)
- excessive use of uterine tocolytics
- more common in grand multiparous women (lax uterine ligaments)
- 1/1500-1/2000 deliveries

### Clinical Features
- can cause profound vasovagal response with bradycardia, vasodilation, and hypovolemic shock
- shock may be disproportionate to maternal blood loss

### Management
- urgent management essential, call anesthesia
- ABCs: initiate IV crystalloids
- can use tocolytic drug (see *Preterm Labour*, OB16) or nitroglycerin IV to relax uterus and aid replacement
- replace uterus without removing placenta
- remove placenta manually and withdraw slowly
- IV oxytocin infusion (only after uterus replaced)
- re-explore uterus
- may require general anesthetic ± laparotomy

## Postpartum Pyrexia

### Definition
- fever >38°C on any 2 of the first 10 d postpartum, except the 1st day

### Etiology
- endometritis
- wound infection (check C/S and episiotomy sites)
- mastitis/engorgement
- UTI
- atelectasis
- pneumonia
- DVT or pelvic thrombophlebitis

**Etiology of Postpartum Pyrexia**

**B-5W**
**B**reast: engorgement, mastitis
**W**ind: atelectasis, pneumonia
**W**ater: UTI
**W**ound: episiotomy, C/S site infection
**W**alking: DVT, thrombophlebitis
**W**omb: endometritis

### Investigations
- detailed history and physical exam, relevant cultures
- for endometritis: blood and genital cultures
- serum lactic acid for early detection of sepsis

### Treatment
- depends on etiology
  - infection: empiric antibiotics, adjust when sensitivities available
- endometritis: clindamycin + gentamicin IV
- mastitis: cloxacillin or cephalexin
- wound infection: cephalexin + frequent sitz baths for episiotomy site infection
  - DVT: anticoagulants
- prophylaxis against post-C/S endometritis: administer 2 g cefazolin IV 30 min prior to skin incision

**Risk Factors for Endometritis**
C/S, intrapartum chorioamnionitis, prolonged labour, prolonged ROM, multiple vaginal examinations

### ENDOMETRITIS
- definition: inflammation of the endometrium most commonly due to infection
- clinical features: fever, chills, abdominal pain, uterine tenderness, foul-smelling vaginal discharge, or lochia
- treatment: depends on infection severity; oral antibiotics if well, IV antibiotics with hospitalization in moderate to severe cases

### VENOUS THROMBOEMBOLISM
- see *Venous Thromboembolism*, OB30

# Mastitis

- **definition**: inflammation of mammary glands
- must rule out inflammatory carcinoma, as indicated
- differentiate from mammary duct ectasia: mammary duct(s) beneath nipple clogged and dilated ± ductal inflammation ± nipple discharge (thick, grey to green), often postmenopausal women

**Table 23. Lactational vs. Non-Lactational Mastitis**

| | Lactational | Non-Lactational |
|---|---|---|
| **Epidemiology** | More common than non-lactational<br>Often 2-3 wk postpartum | Periductal mastitis most common<br>Mean age 32 yr |
| **Etiology** | *S. aureus* | May be sterile<br>May be infected with *S. aureus* or other anaerobes<br>Smoking is risk factor<br>May be associated with mammary duct ectasia |
| **Symptoms** | Unilateral localized pain<br>Tenderness<br>Erythema | Subareolar pain<br>May have subareolar mass<br>Discharge (variable colour)<br>Nipple inversion |
| **Treatment** | Heat or ice packs<br>Continued nursing/pumping<br>Antibiotics (cloxacillin/cephalexin) (erythromycin if penicillin-allergic) | Broad-spectrum antibiotics and I&D<br>Total duct excision (definitive) |
| **Abscess** | Fluctuant mass<br>Purulent nipple discharge<br>Fever, leukocytosis<br>Discontinue nursing, IV antibiotics (nafcillin/oxacillin), I&D usually required | If mass does not resolve, fine-needle aspiration to exclude cancer and U/S to assess presence of abscess<br>Treatment includes antibiotics, aspiration, or I&D (tends to recur)<br>May develop mammary duct fistula<br>A minority of non-lactational abscesses may occur peripherally in breast with no associated periductal mastitis (usually *S. aureus*) |

# Postpartum Mood Alterations

## POSTPARTUM BLUES

- 40-80% of new mothers, onset day 3-10; extension of the "normal" hormonal changes and adjustment to a new baby
- self-limited, should resolve by 2 wk
- manifested by mood lability, depressed affect, increased sensitivity to criticism, tearfulness, fatigue, irritability, poor concentration/despondency, anxiety, and insomnia

## POSTPARTUM DEPRESSION

- **definition**: major depression occurring in a woman within 6 mo of childbirth (see Psychiatry, PS12)
- **epidemiology**: 10-15%, risk of recurrence 50%
- **risk factors**
  - personal or family history of depression (including PPD)
  - prenatal depression or anxiety
  - stressful life situation
  - poor support system
  - unwanted pregnancy
  - colicky or sick infant
- **clinical features**: suspect if the "blues" last beyond 2 wk, or if the symptoms in the first 2 wk are severe (e.g. extreme disinterest in the baby, suicidal or homicidal/infanticidal ideation)
- **assessment**: Edinburgh Postnatal Depression Scale or others
- **treatment**: antidepressants, psychotherapy, supportive care, and ECT if refractory
- **prognosis**: interferes with bonding and attachment between mother and baby, so it can have long-term effects

## POSTPARTUM PSYCHOSIS

- **definition**: onset of psychotic symptoms over 24-72 h within first month postpartum, can present in the context of depression
- **epidemiology**: rare (0.2%)

# Postpartum Care

## Postpartum Office Visit at 6 Weeks

### Care of Mother (The 10 Bs)

- **B**e careful: do not use douches or tampons for 4-6 wk post-delivery
- **B**e fit: encourage gradual increases in walking, Kegel exercises
- **B**irth control: assess for use of contraceptives
- **B**reastfeeding is NOT an effective method of birth control (see Gynecology, GY15, for more detail about different contraceptive options postpartum)
- **B**ladder: assess for urinary incontinence, maintain high fluid intake
- **B**lood pressure: especially if gestational HTN
- **B**lood tests: CBC (for anemia if had PPH)
- **B**lues: (see *Postpartum Mood Alterations*, OB47)
- **B**owel: fluids and high-fibre foods, bulk laxatives; for hemorrhoids/perineal tenderness: pain meds, doughnut cushion, sitz baths, and ice compresses
- **B**reast and pelvic exam: watch for Staphylococcal or Streptococcal mastitis/abscess, ± Pap smear at 6 wk if due for screening



The acronym "**BUBBLES**" for what to ask about when rounding on postpartum care. Modify this for C/S or vaginal delivery

**B**aby care and breastfeeding-- Latch? Amount?
**U**terus – firm or boggy?
**B**ladder function – Voiding well? Dysuria?
**B**owel function – Passing gas or stool? Constipated?
**L**ochia or discharge – Any blood?
**E**pisiotomy/laceration/incision – Pain controlled?
**S**ymptoms of VTE – Dyspnea? Calf pain?

### Physiological Changes Postpartum

- uterus weight rapidly diminishes through catabolism, cervix loses its elasticity and regains firmness
  - should involute ~1 cm below umbilicus per day in first 4-5 d, reaches non-pregnant state in 4-6 wk postpartum
- ovulation resumes in ~45 d after giving birth, non-lactating women usually ovulate sooner than lactating women
- lochia: normal vaginal discharge postpartum, uterine decidual tissue sloughing
  - decreases and changes in colour from red (lochia rubra; presence of erythrocytes, 3-4 d) → pale (lochia serosa) → white/yellow (lochia alba; residual leukorrhea) over 3-6 wk
- foul-smelling lochia suggests endometritis

### Breastfeeding Problems

- inadequate milk: consider domperidone
- breast engorgement: cool compress, manual expression/pumping
- nipple pain: clean milk off nipple after feeds, moisturizer, topical steroid if needed
- mastitis: treat promptly (see *Postpartum Pyrexia*, OB46)
- inverted nipples: makes feeding difficult
- maternal medications: may require pediatric consultation (see *Breastfeeding and Drugs*, OB48)

### Bladder Dysfunction

- pelvic floor prolapse can occur after vaginal delivery
- stress or urge urinary incontinence common
- increased risk with instrumental delivery or prolonged second stage
- conservative management for stress and urge incontinence: pelvic floor retraining with Kegel exercises/pelvic physiotherapy, vaginal cones or pessaries, and lifestyle modifications (e.g. limit fluid, caffeine intake)
- surgical management for stress incontinence: midurethral slings including retropubic tension free vaginal tape (TVT) or transobturator tape (TOT), retropubic urethropexy (Burch), urethral bulking

### Puerperal Pain

- "after pains" common in first 3 d due to uterine contractions; encourage simple analgesia
- ice packs can be used on perineum if painful
- encourage regular analgesia and stool softener

# Breastfeeding and Drugs

**Table 24. Drug Safety During Breastfeeding**

| Safe During Breastfeeding | Contraindicated When Breastfeeding |
|---|---|
| Analgesics (e.g. acetaminophen, NSAIDs) | Chloramphenicol (bone marrow suppression) |
| Anticoagulants (e.g. heparin) | Cyclophosphamide (immune system suppression) |
| Antidepressants (e.g. sertraline, fluoxetine, tricyclic antidepressants) | Sulphonamides (in G6PD deficiency, can lead to hemolysis) |
| Antiepileptics (e.g. phenytoin, carbamazepine, valproic acid) | Nitrofurantoin (in G6PD deficiency, can lead to hemolysis) |
| Antihistamines | Tetracycline |
| Antimicrobials (e.g. penicillins, aminoglycosides, cephalosporins) | Lithium |
| β-adrenergics (e.g. propanolol, labetalol) | Phenindione |
| Insulin | Bromocriptine |
| Steroids | Anti-neoplastics and immunosuppresants |
| OCP (low dose) – although may decrease breast milk production | Psychotropic drugs (relative contraindication) |

# Common Medications

**Table 25. Common Medications**

| Drug Name (Brand Name) | Dosing Schedule | Indications/Comments |
|---|---|---|
| **betamethasone valerate (Celestone®)** | 12 mg IM q24h x 2 doses | Enhancement of fetal pulmonary maturity for PTL |
| **carboprost (Hemabate®)** | 0.25 mg IM/IMM q15min<br>Max 2 mg | Treatment of uterine atony |
| **cefazolin** | 2 g IV then 1 g q8h | GBS prophylaxis (penicillin allergic and not at risk for anaphylaxis) |
| **clindamycin** | 900 mg IV q8h | Used in endometritis |
| **dexamethasone** | 6 mg IM q12h x 4 doses | Enhancement of fetal pulmonary maturity for PTL |
| **dinoprostone (Cervidil®: PGE2 impregnated thread)** | 10 mg PV (remove after 12 h)<br>Max 3 doses | Induction of labour<br>Advantage: can remove if uterine hyperstimulation |
| **doxylamine succinate (Diclectin®)** | 2 tabs qhs + 1 tab qam + 1 tab qpm<br>Max 8 tabs/d | Each tablet contains 10 mg doxylamine succinate with vitamin B6<br>Used first-line for N/V in pregnancy, including hyperemesis gravidarum |
| **erythromycin** | 500 mg IV q6h | GBS prophylaxis (penicillin allergic and at risk for anaphylaxis) |
| **folic acid** | 0.4-1 mg PO OD x 1-3 mo preconception and T1<br>5 mg PO OD with past Hx of NTD/risks for NTD | Prevention of ONTD |
| **methotrexate** | 50 mg/mL IM or 50 mg PO x 1 dose | For ectopic pregnancy or medical abortion |
| **methylergonavine maleate (Ergotamine®)** | 0.25 mg IM/IMM q15min up to 1.25 mg<br>or IV bolus 0.125 mg | Treatment of uterine atony |
| **misoprostol (Cytotec®)** | 600-1000 µg PR x 1 dose<br>400 µg PO/SL x 1 dose<br>or 800 µg PV x 1 dose 3-7 d after methotrexate | For treatment of PPH<br>For medical abortion/retained products of conception |
| **oxytocin (Pitocin®)** | 0.5-2.0 mU/min IV or 10 U/L NS increase by 1-2 mU/min q20-60min<br>Max 36-48 mU/min<br>10 IU IM at delivery of anterior shoulder and of placenta<br>20 IU/L NS or RL IV continuous infusion | Augmentation of labour (also induction of labour)<br>Prevention of uterine atony<br>Treatment of uterine atony |
| **Penicillin G** | 5 million IU IV, then 2.5 million IU IV q4h until delivery | GBS prophylaxis |
| **PGE2 gel (Prostin® gel)** | 0.5 mg PV q6-12h; max 3 doses | Induction of labour |
| **Rh IgG (Rhogam®)** | 300 µg IM x 1 dose | Given to Rh-negative women<br>Routinely at 28 wk GA<br>Within 72 h of birth of Rh+ fetus<br>Positive Kleihauer-Betke test<br>With any invasive procedure in pregnancy<br>Ectopic pregnancy<br>Antepartum hemorrhage<br>Miscarriage or therapeutic abortion (dose: 50 µg IM only) |

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# OP Ophthalmology

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# Acronyms

| | |
|---|---|
| AION | anterior ischemic optic neuropathy |
| AMD | age-related macular degeneration |
| BCVA | best-corrected visual acuity |
| BRAO | branch retinal artery occlusion |
| BRVO | branch retinal vein occlusion |
| C:D | cup to disc ratio |
| CMV | cytomegalovirus |
| CRAO | central retinal artery occlusion |
| CRVO | central retinal vein occlusion |
| D | diopter |
| DM | diabetes mellitus |
| DR | diabetic retinopathy |
| EBV | Epstein-Barr virus |
| EOM | extraocular movement |
| FML | fluorometholone |
| GAT | Goldmann applanation tonometry |
| GCA | giant cell arteritis |
| GPC | giant papillary conjunctivitis |
| HRT | Heidelberg retinal tomography |
| INO | internuclear ophthalmoplegia |
| IOL | intraocular lens |
| IOP | intraocular pressure |
| LASIK | laser-assisted in situ keratomileusis |
| MS | multiple sclerosis |
| OCT | optical coherence tomography |
| OHT | ocular hypertension |
| PACG | primary angle-closure glaucoma |
| PDR | proliferative diabetic retinopathy |
| PDT | photodynamic therapy |
| PERRLA | pupils equal, round, and reactive to light and accommodation |
| POAG | primary open-angle glaucoma |
| PRK | photorefractive keratectomy |
| PVD | posterior vitreous detachment |
| RA | rheumatoid arthritis |
| RAPD | relative afferent pupillary defect |
| RD | retinal detachment |
| ROP | retinopathy of prematurity |
| RPE | retinal pigment epithelium |
| SLE | systemic lupus erythematosus |
| SPK | superficial punctate keratitis |
| TIA | transient ischemic attack |
| VA | visual acuity |
| VEGF | vascular endothelial growth factor |
| YAG | yttrium aluminium garnet |

# Basic Anatomy Review

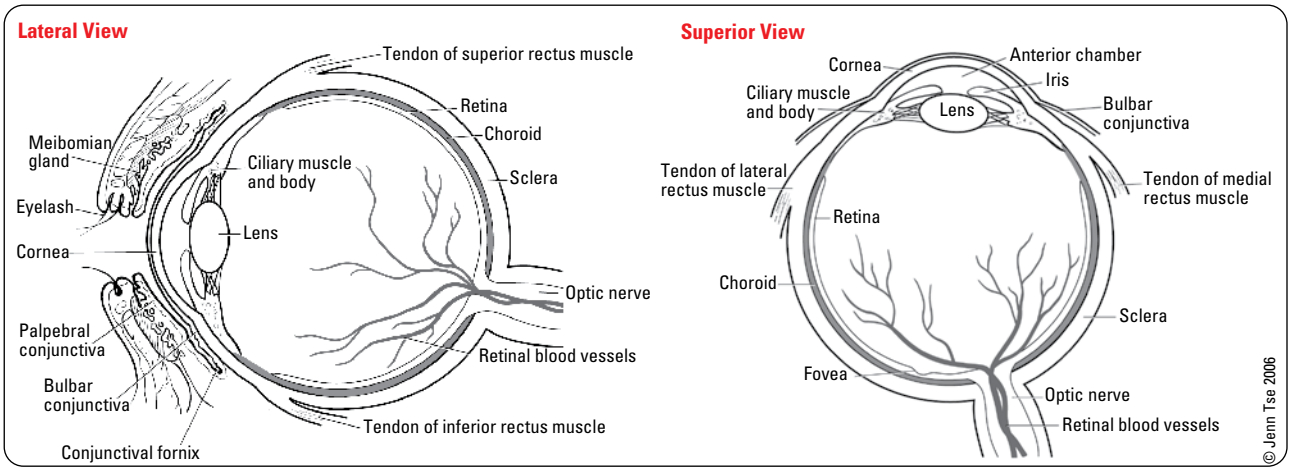



**Figure 1. Anatomy of the eye**

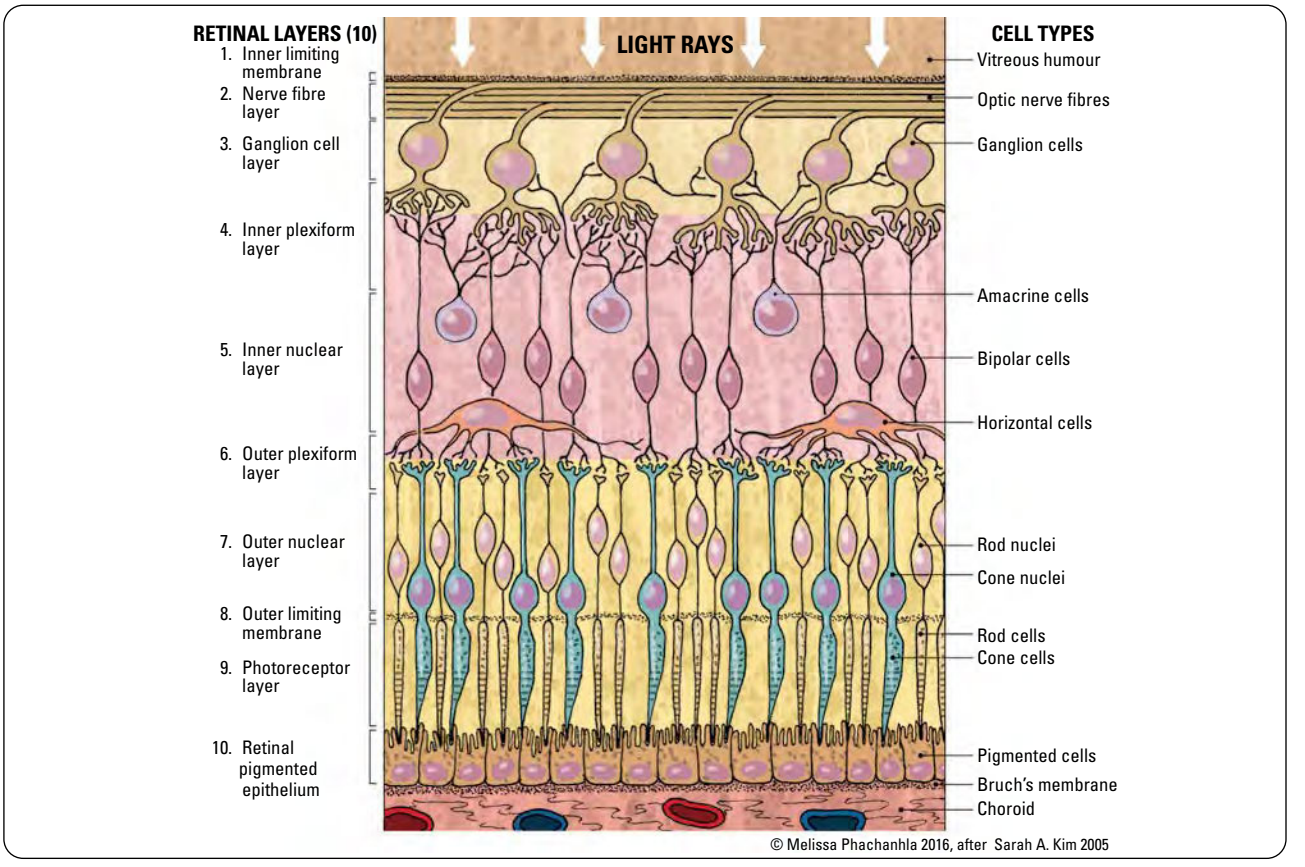



**Figure 2. Layers of the retina**

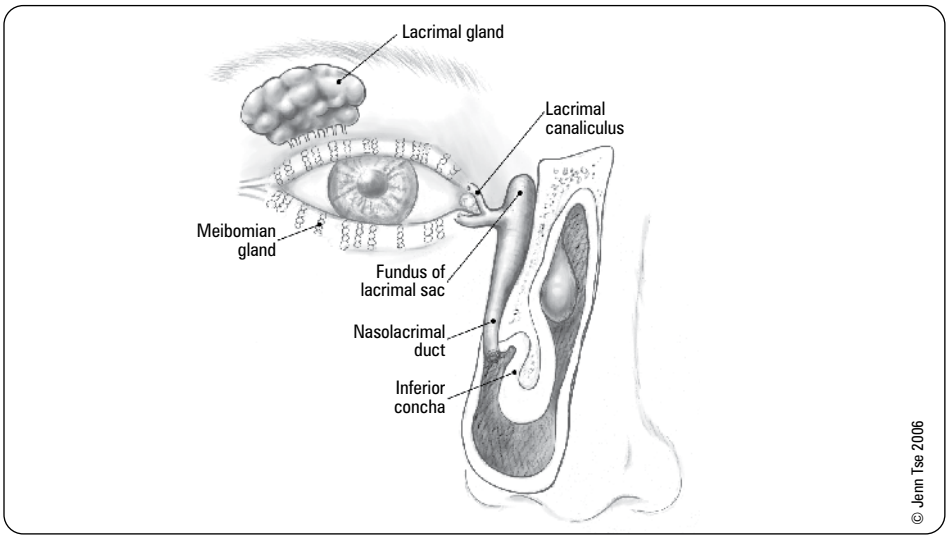



**Figure 3. Tear drainage from the eye (lacrimal apparatus)**

# Differential Diagnoses of Common Presentations

## Loss of Vision

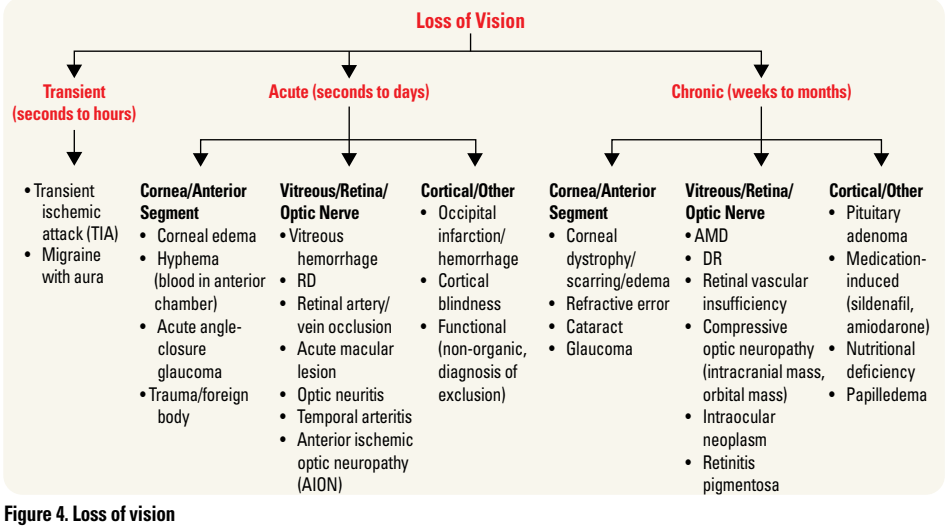



**Figure 4. Loss of vision**

## Red Eye

**Table 1. Common Causes of Red Eye**

| | | |
|---|---|---|
| **Lids/Orbit/Lacrimal System**<br>Hordeolum/chalazion<br>Blepharitis<br>Entropion/ectropion<br>Foreign body/laceration<br>Dacryocystitis/dacryoadenitis | **Cornea**<br>Foreign body (including contact lens)<br>Keratitis<br>Abrasion, laceration<br>Ulcer | **Other**<br>Trauma<br>Post-operative endophthalmitis<br>Pharmacologic (e.g. prostaglandin analogs) |
| **Conjunctiva/Sclera**<br>Subconjunctival hemorrhage<br>Conjunctivitis<br>Dry eyes<br>Pterygium<br>Episcleritis/scleritis<br>Preseptal/orbital cellulitis | **Anterior chamber**<br>Anterior uveitis (iritis, iridocyclitis)<br>Acute glaucoma<br>Hyphema (blood in anterior chamber)<br>Hypopyon (pus in anterior chamber) | |

**Table 2. Common Differential Diagnoses of Red Eye**

| | Conjunctivitis | Acute Iritis | Acute Glaucoma | Keratitis (Corneal Abrasion/Ulcer) |
|---|---|---|---|---|
| **Discharge** | Bacterial: purulent<br>Viral: serous/mucoid<br>Allergic: mucoid | No | Clear | |
| **Pain** | ± | ++ (dull/achy) | +++ (nausea) | ++ (sharp) |
| **Photophobia** | No | +++ | + | ++ |
| **Blurred Vision** | No | ++ | +++ | Varies |
| **Pupil** | Normal | Smaller | Fixed in mid-dilation | Same or smaller |
| **Injection** | Diffuse conjunctival injection involving the bulbar conjunctiva for 360 + palpebral or tarsal conjunctiva | Ciliary flush (peri-limbal) | Conjunctival injection | Possible conjunctival injection |
| **Cornea** | Normal (subepithelial infiltrates in adenoviral conjunctivitis) | Keratic precipitates | Cloudy | Infiltrate, edema, and may have keratic precipitates |
| **IOP** | Normal | Varies | Increased markedly | Normal or slightly decreased |
| **Anterior Chamber** | Normal | +++ Cells and flare | Shallow | Cells and flare or normal |
| **Nausea and Vomiting** | No | No | +++ | No |
| **Other** | Large, tender pre-auricular node(s) if viral | Posterior synechiae | Coloured halos, nausea and vomiting | |



Not every red eye has conjunctivitis

# Vision Pain

### Differential Diagnosis - Acute

- vitreous hemorrhage
- retinal artery/vein occlusion
- RD
- AION
- optic neuritis
- amaurosis fugax/TIA/stroke

### Differential Diagnosis - Chronic

- cataract
- refractive error
- corneal dystrophy
- glaucoma
- AMD
- DR

# Ocular Pain

- differentiate from eye fatigue (asthenopia)
- ocular surface disease
- herpes zoster prodrome
- trauma/foreign body
- blepharitis
- keratitis
- corneal abrasion/ulcer
- acute glaucoma
- acute uveitis
- scleritis
- episcleritis
- optic neuritis

# Floaters

- PVD (often secondary to age-related vitreous syneresis)
- vitreous hemorrhage
- retinal tear/detachment
- intermediate uveitis (pars planitis)
- posterior uveitis (chorioretinitis)

# Flashes of Light (Photopsia)

- PVD (often secondary to age-related vitreous syneresis)
- retinal tear/detachment
- migraine with aura

# Photophobia (Severe Light Sensitivity)

- corneal abrasion, corneal ulcer
- keratitis
- acute angle-closure glaucoma
- iritis
- meningitis/encephalitis
- migraine
- subarachnoid hemorrhage (SAH)

# Diplopia (Double Vision)

**Table 3. Common Causes of Diplopia**

| Binocular Diplopia | Monocular Diplopia |
|---|---|
| **Definition** | |
| Occurs with both eyes open, eliminated with occlusion of either eye | Occurs with one eye open, remains with occlusion of unaffected eye |
| **Causes** | |
| Congenital: strabismus syndromes | Optical factors: refractive error/astigmatism |
| Ocular motor nerve dysfunction: III, IV, VI Nerve Palsy | Mechanical process: dislocated lens, postoperative sequelae (cataract surgery, peripheral laser iridotomy) |
| Neuromuscular junction disease: myasthenia gravis, botulism | Other: strands of mucus in tear film (keratoconus) |
| Mechanical process: muscle restriction/entrapment, thyroid ophthalmopathy | |
| **Supranuclear Causes: INO (multiple sclerosis, brainstem infarct)** | |

# Ocular Problems in the Contact Lens Wearer

- solution hypersensitivity
- tight lens syndrome
- corneal abrasion
- giant papillary conjunctivitis/contact lens allergy
- SPK from dry eyes
- limbal stem cell deficiency
- corneal neovascularization
- sterile corneal infiltrates (immunologic)
- infected ulcers (*Pseudomonas*, *Acanthamoeba*)

# Ocular Emergencies

**These require urgent ophthalmology consultation for management**

### Sight-Threatening

- lid laceration
- globe rupture
- chemical burn
- corneal ulcer
- gonococcal conjunctivitis
- acute iritis
- acute glaucoma
- CRAO
- intraocular foreign body
- RD (especially when macula threatened)
- endophthalmitis
- GCA

### Life-Threatening

- proptosis (rule out cavernous sinus fistula or thrombosis)
- CN III palsy with dilated pupil (intracranial aneurysm or externally compressive neoplastic lesion)
- papilledema (elevated or increased ICP workup)
- orbital cellulitis
- leukocoria: white reflex (absent red reflex, must rule out retinoblastoma, especially in children)

# The Ocular Examination

### Visual Acuity – Distance

- Snellen Acuity = $\frac{\text{testing distance (usually 20 ft or 6 m)}}{\text{smallest line patient can read on the chart}}$
  - e.g. 20/40 = what the patient can see at 20 feet away (numerator) is what a "normal" person can see at 40 feet away (denominator)
- distance visual acuity should be tested with distance glasses on in order to obtain best-corrected visual acuity
- testing hierarchy for low vision: Snellen acuity (20/x) → counting fingers at a given distance (CF) → hand motion (HM) → light perception with projection (LP with projection) → light perception (LP) → no light perception (NLP)
- legal blindness is BCVA that is ≤20/200 in best eye

**Example 1**

$\overline{SC}$ V 20/40 −1
20/80 +2 → 20/25 PH

**Example 2**

$\overline{CC}$ V CF 3'
HM

**Note:** RIGHT EYE visual acuity always listed on top.

| | |
|---|---|
| **V** | Vision |
| **SC** | Without correction |
| **CC** | With correction |
| **20/40 -1** | All except one letter of 20/40 |
| **20/80+2** | All of 20/80 plus two letters of 20/70 |
| **PH** | Visual acuity with pinhole correction |
| **CF** | Counting fingers |
| **HM** | Hand motion |

**Figure 5. Ophthalmology nomenclature for visual acuity**

OD = oculus dexter = right eye
OS = oculus sinister = left eye
OU = oculus uterque = both eyes

Snellen visual acuity of 20/20 equates to "normal" vision

**Normal Infant and Child Visual Acuity**

- 6-12 mo: 20/120
- 1-2 yr: 20/80
- 2-4 yr: 20/20

- minimum visual requirements to operate a non-commercial automobile in Ontario are: 20/50 BCVA with both eyes open and examined together, 120° continuous horizontal visual field, and 15° continuous visual field above and below fixation

### Visual Acuity – Near
- use pocket vision chart (Rosenbaum Pocket Vision Screener)
- record Jaeger (J) or Point number and testing distance (usually 30 cm) e.g. J2 @ 30 cm
- conversion to distance visual acuity possible (e.g. immobile patient, no distance chart available)

### Visual Acuity for Infants, Children, Non-English Speakers, and Dysphasics
- newborns
  - VA cannot be tested conventionally
- 3 mo-3 yr: can only assess visual function, not acuity
  - test each eye for fixation symmetry using an interesting object
  - normal function noted as "CSM" = central, steady, and maintained
- 3 yr until alphabet known
  - pictures or letter cards/charts such as HOTV or Sheridan-Gardiner test (children point to optotypes on a matching card)
  - tumbling "E" chart

### Colour Vision
- test with Ishihara pseudoisochromatic plates
- record number of correctly identified plates presented to each eye, specify incorrect plates
- important for testing optic nerve function (e.g. optic neuritis, chloroquine use, thyroid ophthalmopathy)
- note: red-green colour blindness is sex-linked and occurs in 7-10% of males

## VISUAL FIELDS
- test "visual fields by confrontation" (4 quadrants, each eye tested separately) for estimation of visual field loss
- accurate, quantifiable assessment with automated visual field testing (Humphrey or Goldmann) or Tangent Screen
- use Amsler grid (each eye tested separately) to check for central or paracentral scotomas (blind spots) in patients with AMD

## PUPILS
- use reduced room illumination with patient focusing on distant, fixed object to prevent near reflex
- examine pupils for shape, size, symmetry, and reactivity to light (both direct and consensual response)
- test for RAPD with swinging flashlight test, check by reverse RAPD test if one pupil non-reactive
- test pupillary constriction portion of near reflex by bringing object close to patient's nose
- "normal" pupil testing often noted as PERRLA (pupils equal, round, reactive to light and accommodation)

## ANTERIOR CHAMBER DEPTH
- shine light tangentially from temporal side
- if >2/3 of nasal side of iris in shadow → shallow anterior chamber

### The Van Herick Method (Slit Lamp technique)
- shine thin-angled slit beam onto the peripheral cornea of each eye, view at a 60° angle from the beam
- estimate depth between the posterior surface of the cornea and the iris as a proportion of corneal thickness
- ratios ≤1/4 implies risk of occludable angle; however, if >1/4, this does not rule out risk
- gonioscopy, as performed by an ophthalmologist, is gold-standard for assessing anterior chamber depth

## EXTRAOCULAR MUSCLES

### Alignment
- Hirschberg corneal reflex test
  - examine in primary position of gaze (i.e. straight ahead) with patient focusing on distant object
  - shine light into patient's eyes from ~30 cm away
  - corneal light reflex should be at the same position on each cornea
- strabismus testing as indicated (cover test, cover-uncover test, prism testing) (see *Strabismus*, OP36)

### Movement
- examine movement of eyeball through six cardinal positions of gaze
- ask patient if diplopia or pain is present in any position of gaze
- observe for horizontal, vertical, or rotatory nystagmus (rhythmic, oscillating movements of the eye)
- resolving horizontal nystagmus at end-gaze is usually normal

### Diplopia
- see Neurology, N16

Test pupils using an ophthalmoscope focused on the red reflex; this will provide a better view than using a penlight

**4 Ps of Inspection**
**P**upil: shape, size, symmetry
**P**osition: esotropia, exotropia, central
**P**tosis
**P**rimary nystagmus

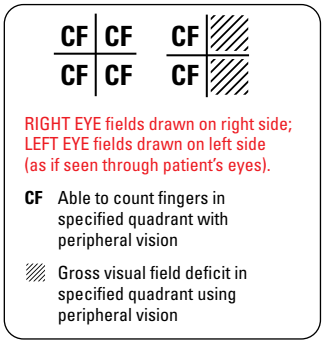



**Figure 6. Ophthalmology nomenclature for visual fields by confrontation**

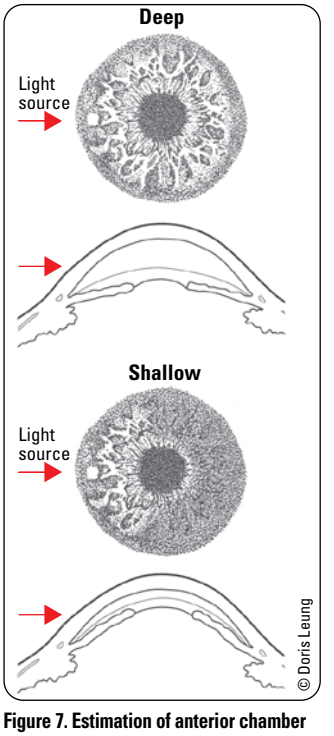



**Figure 7. Estimation of anterior chamber depth**

## SLIT-LAMP EXAMINATION

### Ocular Adnexa
- lids, lashes, lacrimal system

### Anterior Segment
- conjunctiva / sclera
- cornea
  - fluorescein dye: stains de-epithelialized cornea; dye appears fluorescent green with cobalt blue filtered light
  - Rose Bengal dye: stains devitalized corneal epithelium
- anterior chamber/angle (Van Herick)
- iris/pupil
- lens (assess for cataract)
- anterior vitreous

### Posterior Segment (requires 78D or 90D lens)
- vitreous
- optic disc (colour, C:D ratio, sharpness of disc margin)
- macula (~1.5-2 disc diameters temporal to disc), fovea (foveal light reflex)
- retinal vessels
- retinal background

## TONOMETRY
- measurement of IOP
- normal range is 9-21 mmHg (average 15 mmHg)
- IOP has diurnal variation, so always record the time of day at which the measurement was taken
- commonly measured by:
  - GAT: clinical gold standard, performed using the slit-lamp with special tip (prism)
  - Tono-Pen®: benefit is portability and use of disposable probe tips; use when GAT is inaccurate, such as when the cornea is scarred or asymmetric
  - non-contact tonometer (NCT): air puff, least reliable
- use topical anesthetic for GAT and Tono-Pen®; apply fluorescein dye and use cobalt blue light for GAT

## DIRECT OPHTHALMOSCOPY
- best performed with pupils dilated (for list of mydriatics and cycloplegics see Table 13, OP42)
  1. assess red reflex
     - light reflected off the retina produces a "red reflex" when viewed from ~1 foot away
     - anything that interferes with the passage of light will diminish the red reflex (e.g. large vitreous hemorrhage, cataract, retinoblastoma)
  2. examine the posterior segment of the eye
     - vitreous
     - optic disc (colour, C:D ratio, sharpness of disc margin)
     - macula (~1.5-2 disc diameters temporal to disc), fovea (foveal light reflex)
     - retinal vessels
     - retinal background
- contraindications to pupillary dilatation
  - shallow anterior chamber – can precipitate acute angle-closure glaucoma
  - iris-supported anterior chamber lens implant
  - potential neurologic abnormality requiring pupil evaluation
  - use caution with cardiovascular disease – mydriatics may cause tachycardia and HTN

# Optics

## REFRACTION
- two techniques used
  - flash/streak retinoscopy: refractive error determined objectively by the examiner using lenses and retinoscope
  - manifest: subjective trial using loose lenses or a phoropter (device the patient looks through that is equipped with lenses)
  - cycloplegic: manifest refraction with accommodation temporarily paralyzed with cycloplegics
- a typical lens prescription would contain:
  - sphere power in diopter (measurement of refractive power of lens, equal to reciprocal of focal length in metres)
  - cylinder power in diopter to correct astigmatism
  - axis of cylinder in degrees
  - "add" (bifocal/progressive reading lens) for presbyopes
  - e.g. -1.50 + 1.00 x 120°, add +2.00

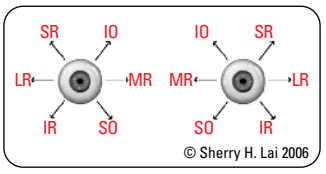


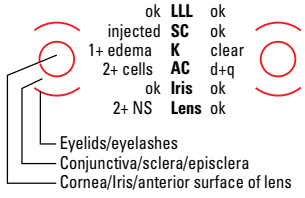

**Figure 8. Diagnostic positions of gaze for isolated primary actions of extraocular muscles**

**Extraocular Muscle Innervations**

**LR6 SO4 AE3**
**L**ateral **R**ectus via CN **VI**
**S**uperior **O**blique via CN **IV**
**A**ll **E**lse via CN **III** (superior, medial, and inferior rectus, inferior oblique)

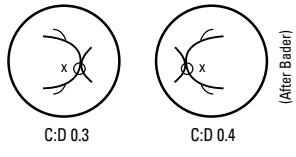
**Aqueous Flare**
- Resembles dust particles in a beam of light
- Results from protein leaking from blood vessels
- Distinguish from aqueous cells (individual cells in anterior chamber)

**Note:** RIGHT EYE drawn on the left, LEFT EYE drawn on the right (as if looking at patient's face)




| | |
|---|---|
| **LLL** | Lids, lashes, lacrimal |
| **SC** | Sclera, conjunctiva |
| **K** | Cornea |
| **AC** | Anterior chamber |
| **d+q** | Deep (not shallow) and quiet (no cells in AC) |
| **NS** | Nuclear sclerosis (cataract) |

ⓃD/M/V
(normal disc, macula, vessels)




C:D 0.3 C:D 0.4

| | |
|---|---|
| C:D | Cup : Disc ratio |
| x | Fovea |

Any abnormality or pathology is drawn on the sketch in the appropriate location, and is labelled (e.g. trichiasis, conjunctivitis/episcleritis/scleritis, corneal abrasion/ulcer, foreign body, etc.)

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**Figure 9. Slit-lamp examination note**




**Note:** RIGHT EYE IOP always listed on top. Always include time.

Note method used to measure IOP (GAT, Tono-Pen®, airpuff).

**Figure 10. Tonometry**

## REFRACTIVE EYE SURGERY

- permanently alters corneal refractive properties by ablating tissue to change curvature of the cornea
- used for correction of myopia, hyperopia, and astigmatism
- common types include PRK and LASIK
- potential risks/side-effects: infection, under/overcorrection, increased glare/halo perception at night, corneal haze (PRK only), dry eyes (more common in LASIK than PRK), regression, and flap complications such as free cap (loss of flap), traumatic flap dislocations, buttonhole flap, and epithelial ingrowth (LASIK only)

**Central Corneal Thickness (CCT)**
Average CCT = 550 µm
By GAT, IOP is over-estimated with thick corneas and under-estimated with thin corneas

### Table 4. Optics

| | Pathophysiology | Clinical Features | Treatment | Complications |
|---|---|---|---|---|
| **Emmetropia** | Image of distant objects focus exactly on the retina | No refractive error | | |
| **Myopia** | Globe too long relative to refractive mechanisms, or refractive mechanisms too strong<br>Light rays from distant object focus in front of retina → blurring of (distance) vision | "Nearsightedness"<br>Usually presents in 1st or 2nd decade, stabilizes in 2nd and 3rd decade; rarely begins after age 25 except in patients with DM or cataracts<br>Blurring of distance vision; near vision usually unaffected<br>Prevalence: 30-40% in U.S. population; higher among Asians | Correct with negative diopter/concave/"negative" lenses to diverge light rays<br>Refractive eye surgery | Retinal tear/detachment, myopic maculoschisis leading to formation of macular hole, open-angle glaucoma<br>Other complications that are not prevented with refractive correction |
| **Hyperopia** | Globe too short relative to refractive mechanisms, or refractive mechanisms too weak<br>Light rays from distant object focus behind retina → blurring of near ± distant vision<br>May be developmental or due to any etiology that shortens globe | "Farsightedness"<br>Youth: usually do not require glasses (still have sufficient accommodative ability to focus image on retina), but may develop accommodative esotropia (see *Strabismus*, OP36)<br>30s-40s: blurring of near vision due to decreased accommodation, may need reading glasses<br>>50s: blurring of distance vision due to severely decreased accommodation | When symptomatic, correct with positive diopter/convex/"plus" lenses to converge light rays<br>Refractive eye surgery | Angle-closure glaucoma, particularly later in life as lens enlarges |
| **Astigmatism** | Light rays not refracted uniformly in all meridians due to non-spherical surface of cornea or non-spherical lens (e.g. football-shaped)<br>**Two types**<br>Regular – curvature uniformly different in meridians at right angles to each other<br>Irregular – distorted cornea caused by injury, keratoconus (cone-shaped cornea), corneal scar, or severe dry eye | Affects ~30% of population, with prevalence increasing with age<br>Mild astigmatism unnoticeable<br>Higher amounts of astigmatism may cause blurry vision, squinting, asthenopia, or headaches | Correct with cylindrical lens (if regular)<br>Try contact lens (if irregular)<br>Refractive eye surgery | |
| **Presbyopia** | Normal aging process (>40 yr)<br>Hardening/reduced deformability of lens results in decreased accommodative ability<br>Accommodative power is 14D at age 10, diminishes to 3.5D by age 40 yr<br>Near images cannot be focused onto the retina (focus is behind the retina as in hyperopia) | If initially emmetropic, person begins to hold reading material farther away, but distance vision remains unaffected<br>If initially myopic, person removes distance glasses to read<br>If initially hyperopic, symptoms of presbyopia occur earlier | Correct with positive diopter/convex/"plus" lenses for reading | |
| **Anisometropia** | Difference in refractive errors between eyes | | | Second most common cause of amblyopia in children |

**Myopia**

**LMN**
**L**ong globe
**M**yopic
**N**egative correction/**N**earsighted

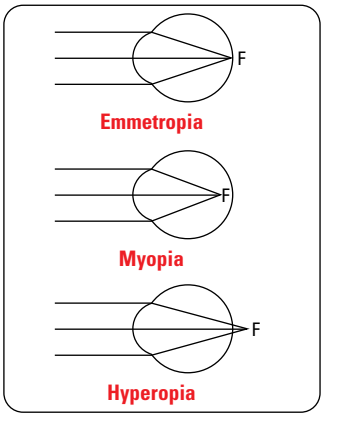



**Figure 11. Emmetropia and refractive errors**

**Structures Responsible for Refractive Power**
- Cornea (2/3)
- Lens (1/3)

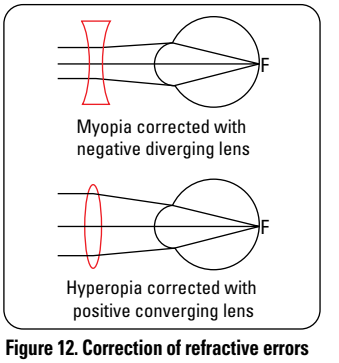



**Figure 12. Correction of refractive errors**

# The Orbit

## Globe Displacement

**Table 5. Exophthalmos (Proptosis) and Enophthalmos**

| | Exophthalmos (Proptosis) | Enophthalmos |
|---|---|---|
| **Definition** | Anterior displacement (protrusion) of the globe<br>Exophthalmos generally refers to an endocrine etiology or protrusion of >18 mm (as measured by a Hertel exophthalmometer)<br>Proptosis generally refers to other etiologies (e.g. cellulitis) or protrusion of <18 mm | Posterior displacement (retraction) of the globe |
| **Investigations** | CT/MRI head/orbits, ultrasound orbits, thyroid function tests | CT/MRI orbits |
| **Etiology** | Note: rule out pseudoexophthalmos (e.g. lid retraction)<br>Graves' disease (unilateral or bilateral, most common cause in adults)<br>Orbital cellulitis (unilateral, most common cause in children)<br>1° or 2° orbital tumour<br>Orbital/retrobulbar hemorrhage<br>Cavernous sinus thrombosis or fistula | "Blow-out" fracture (see *Ocular Trauma*, OP40)<br>Orbital fat atrophy<br>Congenital abnormality<br>Metastatic disease |

## Preseptal Cellulitis

### Definition
- infection of soft tissue anterior to orbital septum

### Etiology
- usually follows periorbital trauma or dermal infection

### Clinical Features

**Table 6. Clinical Features of Preseptal and Orbital Cellulitis**

| Finding | Preseptal Cellulitis | Orbital Cellulitis |
|---|---|---|
| **Fever** | May be present | Present |
| **Lid Edema** | Moderate to severe | Severe |
| **Conjunctival Injection** | Absent | Present |
| **Chemosis** | Absent or mild | Marked |
| **Proptosis** | Absent | Present |
| **Pain on Eye Movement** | Absent | Present |
| **Ocular Mobility** | Normal | Decreased |
| **Vision** | Normal | Diminished ± diplopia |
| **RAPD** | Absent | May be seen if severe |
| **Leukocytosis** | Moderate | Marked |
| **ESR** | Normal or elevated | Elevated |
| **Additional Findings** | Skin infection | Sinusitis, dental abscess |

### Treatment
- systemic antibiotics (suspect *H. influenzae* in children; *S. aureus* or *Streptococcus* in adults)
  - e.g. amoxicillin-clavulanic acid
- if severe or child <1 yr, treat as orbital cellulitis

**Role of Oral Corticosteroids in Orbital Cellulitis**
Am J Ophthalmol 2013;156:178-183
**Purpose**: To evaluate the role of oral corticosteroids as an anti-inflammatory adjunct for the treatment of orbital cellulitis.
**Study**: RCT. Patients with acute onset (within 14 d) of orbital cellulitis with or without abscess. 21 patients total (7 patients in group 1: standard intravenous antibiotics; 14 patients in group 2: adjuvant steroids).
**Results**: Patients in group 2 showed earlier resolution of periorbital edema, conjunctival chemosis, pain, proptosis, and EOM deficits, including decreased duration of intravenous antibiotics and hospital stay ($p<0.05$ for all).
**Conclusion**: The use of oral steroids as an adjunct to intravenous antibiotics for orbital cellulitis may decrease inflammatory symptoms with a low risk of worsening infection.

## Orbital Cellulitis

### Definition
- **OCULAR** and **MEDICAL EMERGENCY**
- inflammation of orbital contents posterior to orbital septum
- common in children, elderly, and immunocompromised

### Etiology
- usually secondary to sinus/facial/tooth infections or trauma, can also arise from preseptal cellulitis

### Clinical Features (see Table 6)

### Treatment
- admit, blood cultures x2, orbital CT, IV antibiotics (ceftriaxone + vancomycin) for 1 wk
- surgical drainage of abscess with close follow-up, especially in children

### Complications
- optic nerve inflammation, cavernous sinus thrombosis, meningitis, brain abscess with possible loss of vision, and death

# Lacrimal Apparatus

- tear film made up of three layers
  - outer oily layer (reduces evaporation): secreted by the meibomian glands
  - middle watery layer (forms the bulk of the tear film): constant secretion from conjunctival glands and reflex secretion by lacrimal gland with ocular irritation or emotion
  - inner mucinous layer (aids with tear adherence to cornea): secreted by conjunctival goblet cells
- tears drain from the eyes through the upper and lower lacrimal puncta → superior and inferior canaliculi → lacrimal sac → nasolacrimal duct → nasal cavity behind inferior concha (Figure 3)

## Dry Eye Syndrome (Keratoconjunctivitis Sicca)

### Definition and Etiology
- aqueous-deficient
  - Sjögren syndrome (autoimmune etiology e.g. RA, SLE)
  - non-Sjögren syndrome (idiopathic age-related disease; lacrimal gland scarring e.g. trachoma; decreased secretion e.g. contact lenses, CN VII palsy, anticholinergics, antihistamines, diuretics, β-blockers)
- evaporative (normal lacrimal function, excessive evaporation of aqueous layer)
  - meibomian gland dysfunction (posterior blepharitis)
  - vitamin A deficiency (xerophthalmia with goblet cell dysgenesis)
  - eyelid abnormalities e.g. ectropion, CN VII palsy (decreased blinking)
  - topical ocular medications with preservatives
  - contact lenses, allergic conjunctivitis
- mixed etiologies are common

### Clinical Features
- dry eyes, red eyes, foreign body sensation, blurred vision, tearing
- slit-lamp exam: decreased tear meniscus, decreased tear break-up time (normally should be 10 s), punctate staining of cornea with fluorescein

### Investigations
- surface damage observed with fluorescein/Rose Bengal staining
- decreased distance in Schirmer's test

### Complications
- erosions and scarring of cornea

### Treatment
- medical: preservative-free artificial tears up to q1h and ointment at bedtime (preservative toxicity becomes significant if used more than 4-6x/d), short course of mild topical corticosteroid, omega-3 fatty acids orally (controversial), and eyelid hygiene for blepharitis
  - for moderate cases, cyclosporine ophthalmic emulsion 0.05% (Restasis®) or lifitegrast 5% (Xiidra®) can be used
- procedural: punctal occlusion (punctal plug insertion), lid taping, tarsorrhaphy (sew lids together) if severe
- treat underlying cause



Long-term use of artificial tears with preservatives should be avoided when treating dry eyes

## Epiphora (Excessive Tearing)

### Etiology
- emotion, pain
- environmental stressor (cold, wind, pollen, sleep deprivation)
- lid/lash malposition: ectropion, entropion, trichiasis
- inflammatory: conjunctivitis, dacryoadenitis, uveitis, keratitis, corneal foreign body
- dry eyes (reflex tearing)
- lacrimal drainage obstruction (congenital failure of canalization, aging, rhinitis, dacryocystitis)
- paradoxical gustatory lacrimation reflex (crocodile tears)



Excessive tearing can be caused by dry eyes – if the tear quality is insufficient, "reflex tearing" may occur

### Investigations
- using fluorescein dye, examine for punctal reflux by pressing on canaliculi
- Jones dye test: fluorescein placed in conjunctival cul-de-sac, and cotton applicator placed in nose to detect flow (i.e. rule out lacrimal drainage obstruction)

### Treatment
- lid repair for ectropion or entropion
- eyelash removal for trichiasis
- punctal irrigation (dilation and irrigation)
- nasolacrimal duct probing (infants)
- tube placement: temporary (Crawford) or permanent (Jones)
- surgical: dacryocystorhinostomy – forming a new connection between the lacrimal sac and the nasal cavity

## Dacryocystitis

### Etiology
- acute or chronic infection of the lacrimal sac
- most commonly due to obstruction of the nasolacrimal duct
- commonly associated with *S. aureus, S. pneumoniae, Pseudomonas* species

### Clinical Features
- pain, swelling, redness over lacrimal sac at medial canthus
- epiphora, crusting, ± fever
- digital pressure on the lacrimal sac may extrude pus through the punctum
- in the chronic form, epiphora may be the only symptom

### Treatment
- warm compresses, nasal decongestants, systemic and topical antibiotics (cephalexin if afebrile; cefazolin if febrile)
- incision and drainage; if chronic, obtain cultures by aspiration
- once infection resolves, consider dacryocystorhinostomy

## Dacryoadenitis

### Etiology
- most commonly seen in children and young adults
- inflammation of the lacrimal gland (outer third of upper eyelid)
- acute causes: *S. aureus*, mumps, EBV, herpes zoster, *N. gonorrhoeae*
- chronic causes (often bilateral): lymphoma, leukemia, sarcoidosis, tuberculosis, thyroid ophthalmopathy

### Clinical Features
- pain, swelling, tearing, discharge, redness of the outer region of the upper eyelid
- chronic form is more common and may present as painless enlargement of the lacrimal gland

### Treatment
- supportive: warm compresses, oral NSAIDs
- systemic antibiotics if bacterial cause
- if chronic, treat underlying disorder

# Lids and Lashes

## Lid Swelling

### Etiology
- commonly due to allergy, with shriveling of skin between episodes
- dependent edema on awakening (e.g. CHF, renal or hepatic failure)
- orbital venous congestion due to mass or cavernous sinus fistula
- dermatochalasis (loose skin due to aging or heredity)
- lid cellulitis, thyroid disease (e.g. myxedema), trauma, and chemosis

## Ptosis

### Definition
- drooping of upper eyelid

### Etiology
- aponeurotic: disinsertion or dehiscence of levator aponeurosis (most common)
  - associated with advancing age, trauma, surgery, pregnancy, chronic lid swelling
- mechanical
  - incomplete opening of eyelid due to mass or scarring
- neuromuscular
  - myasthenia gravis (neuromuscular palsy), myotonic dystrophy
  - CN III palsy
  - Horner's syndrome (see *Constricted Pupil, Horner's Syndrome*, OP30)
- congenital
- pseudoptosis (e.g. dermatochalasis, enophthalmos, contralateral exophthalmos)
- drugs (e.g. high dose opioids, heroin abuse, pregabalin)

### Treatment
- surgery (e.g. blepharoplasty, levator resection, Müller's muscle resection, frontalis sling)

# Trichiasis

### Definition
- eyelashes turned inwards

### Etiology
- may result from entropion, involutional age change, chronic inflammatory lid diseases (e.g. blepharitis), trauma, burns

### Clinical Features
- patient complains of red eye, foreign body sensation, significant discomfort, tearing
- may result in corneal ulceration and scarring

### Treatment
- topical lubrication, repeat eyelash epilation, electrolysis, and cryotherapy

# Entropion

### Definition
- lid margin folds inward towards globe

### Etiology
- involutional (aging)
- cicatricial (herpes zoster, surgery, trauma, burns)
- orbicularis oculi muscle spasm
- congenital

**Testing for Entropion**
Forced lid closure: Ask patient to tighten lid then open. In entropion, lid rolls inwards

### Clinical Features
- tearing, foreign body sensation, and red eye
- most commonly affects lower lid
- may cause corneal abrasions with secondary corneal scarring

### Treatment
- lubricants, evert lid with tape, and surgery

# Ectropion

### Definition
- lid margin folds outward from globe

### Etiology
- involutional (aging)
- paralytic (CN VII palsy)
- cicatricial (burns, trauma, surgery)
- mechanical (lid edema, tumour, herniated fat)
- congenital

**Testing for Ectropion**
Snapback test: Pull eyelid inferiorly. In ectropion, lid remains away from globe

### Clinical Features
- tearing and possibly exposure keratitis

### Treatment
- topical lubrication, eyelid taping overnight, and surgery

# Hordeolum (Stye)

### Definition
- acute inflammation of eyelid gland: either meibomian glands (internal lid), glands of Zeis (modified sweat gland) or Moll (modified sebaceous gland in external lid)

### Clinical Features
- infectious agent is usually *S. aureus*
- painful, red swelling of lid

**Hordeolum vs. Chalazion**
Hordeolums are due to an infectious etiology, whereas chalazions are granulomatous inflammation

### Treatment
- warm compresses, lid care, gentle massage
- topical antibiotics are typically ineffective
- usually resolves within 2 wk, but may require incision and drainage

# Chalazion

### Definition
- chronic granulomatous inflammation of meibomian gland often preceded by an internal hordeolum

### Clinical Features
- acute inflammatory signs are usually absent
- differential diagnosis: basal cell carcinoma, sebaceous cell adenoma, meibomian gland carcinoma

### Treatment
- warm compresses
- if no improvement after 1 mo, consider incision and curettage
- chronic recurrent lesion must be biopsied to rule out malignancy

## Blepharitis

### Definition
- inflammation of lid margins

### Etiology
- anterior blepharitis
  - staphylococcus (*S. aureus*): ulcerative, dry scales
  - seborrheic: no ulcers, greasy scales
- posterior blepharitis
  - meibomian gland dysfunction

### Clinical Features
- itching, tearing, foreign body sensation
- thickened, red lid margins, crusting, discharge with pressure on lids ("toothpaste sign")

### Complications
- recurrent hordeola
- conjunctivitis
- keratitis (from poor tear film)
- corneal ulceration and neovascularization

### Treatment
- warm compresses, lid massages, and lid washing using commercially available eyelid scrub solution
- topical or systemic antibiotics as needed
- if severe, ophthalmologist may prescribe a short course of topical corticosteroids, omega-3 fatty acids

## Xanthelasma

### Definition
- eyelid xanthoma (lipid deposits in dermis of lids)

### Clinical Features and Associations
- appear as pale, slightly elevated yellowish plaques or streaks
- most commonly on the medial upper lids, often bilateral
- associated with hyperlipidemia (~50% of patients)
- common in the elderly, more concerning in the young

### Treatment
- excision for cosmesis only, commonly recurs

# Conjunctiva

- thin, vascular mucous membrane
- bulbar conjunctiva: lines sclera to limbus (junction between cornea and sclera)
- palpebral (tarsal) conjunctiva: lines inner surface of eyelid

## Pinguecula

### Definition
- yellow-white subepithelial deposit of hyaline and elastic tissue adjacent to the nasal or temporal limbus, sparing the cornea

### Clinical Features
- associated with sun and wind exposure, aging
- benign, sometimes enlarges slowly
- may be irritating due to abnormal tear film formation over the deposits
- surgery for cosmesis only
- irritative symptoms may be treated with lubricating drops

## Pterygium

### Definition
- fibrovascular, triangular, wing-like encroachment of epithelial tissue onto the cornea

### Clinical Features
- may induce astigmatism, decrease vision
- excision for chronic inflammation, threat to visual axis, cosmesis
- irritative symptoms may be treated with lubricating drops
- one-third recur after excision, lower recurrence with conjunctival autograft (~5%)

# Subconjunctival Hemorrhage

- blood beneath the conjunctiva, otherwise asymptomatic
- idiopathic or associated with trauma, Valsalva maneuver, bleeding disorders, HTN, anticoagulation
- give reassurance if no other ocular findings, resolves spontaneously in 2-3 wk
- 360° involvement should be highly suspicious for globe rupture if trauma history
- if recurrent, consider medical/hematologic workup

# Conjunctivitis

## Etiology
- infectious
  - bacterial, viral, chlamydial, gonococcal, fungal, and parasitic
- non-infectious
  - allergic, atopic, seasonal, giant papillary conjunctivitis (contact lens wearers)
  - toxic: irritants, dust, smoke, irradiation
  - secondary to another disorder: dacryocystitis, dacryoadenitis, cellulitis, and systemic inflammatory disease

**Types of Discharge**
- Allergic: mucoid
- Viral: watery
- Bacterial: purulent
- Chlamydial: mucopurulent

## Clinical Features
- red eye (conjunctival injection often with limbal pallor), chemosis, and corneal subepithelial infiltrates
- itching, foreign body sensation, tearing, discharge, crusting of lashes in the morning, and lid edema
- ± preauricular and/or submandibular nodes
- follicles: pale lymphoid elevations of the conjunctiva, overlain by vessels
- papillae: fibrovascular elevations of the conjunctiva with central network of finely branching vessels (cobblestone appearance)

- Follicles are usually seen in viral and chlamydial conjunctivitis
- Papillae are usually seen in allergic and bacterial conjunctivitis

## Allergic Conjunctivitis
- associated with rhinitis, asthma, dermatitis, and hay fever
- ocular pruritus, small papillae, chemosis, redness, thickened and erythematous lids
- seasonal (pollen, grasses, plant allergens)

## Treatment
- allergen avoidance, cool compresses, non-preserved artificial tears, topical or oral antihistamine, topical mast cell stabilizer (e.g. cromolyn, ketotifen, olopatadine), and topical corticosteroids

**Antibiotics vs. Placebo for Acute Bacterial Conjunctivitis**
Cochrane DB Syst Rev 2012;9:CD001211
**Purpose**: To assess the benefits and harms of antibiotic therapy in the management of acute bacterial conjunctivitis.
**Criteria**: RCTs with any form of antibiotic treatment compared with placebo including topical, systemic or combined (e.g. antibiotics and steroids) antibiotic treatments.
**Results**: 11 RCTs, 3673 participants. Topical antibiotics improve early (2-5 d) clinical and microbiological remission rates (RR 1.36, 95% CI 1.15-1.61; RR 1.55; 95% CI 1.37-1.76) and benefit clinical remission and microbiological cure rates at a late time point (6-10 d) (RR 1.21, 95% CI 1.10-1.33; RR 1.37, 95% CI 1.24-1.52). By 6-10 d 41% of cases had resolved in the placebo group. No serious outcomes were reported in any group.
**Conclusion**: The use of antibiotic eye drops is associated with modestly improved rates of clinical and microbiological remission in comparison to placebo. Antibiotic eye drops should therefore be considered in order to speed the resolution of symptoms and infection although acute bacterial conjunctivitis is frequently self-limiting.

## Atopic Conjunctivitis
- onset late adolescence and early adulthood with peak between 30-50 yr old
- intense ocular pruritus (perennially), tearing, burning, clear mucus discharge, redness, blurry vision, photophobia, and foreign body sensation
- thickened and intermittent swelling of the eyelids, conjunctival chemosis, conjunctival hyperemia, and tarsal papillary hypertrophy (Figure 13)
- severe cases lead to sub-epithelial fibrosis, fornix foreshortening, and corneal neovascularization

## Treatment
- calcineurin inhibitor ointment (e.g. tacrolimus and pimecrolimus), and topical corticosteroid (clobetasone)

## Giant Papillary Conjunctivitis
- immune reaction to mucus debris on lenses in contact lens wearers
- large papillae form on superior palpebral conjunctiva

## Treatment
- clean, change or discontinue use of contact lens, and topical corticosteroids

## Vernal Conjunctivitis
- large papillae (cobblestones) form on superior palpebral conjunctiva with corneal ulcers and keratitis
- seasonal (warm weather)
- occurs in children, lasts for 5-10 yr then resolves

## Treatment
- non-preserved artificial tears, consider topical steroid, topical cyclosporine (by ophthalmologist)

## Viral Conjunctivitis (pink eye)
- presents with itchiness, pain and swelling
- serous discharge, lid edema, follicles, and pseudomembranes
- subepithelial corneal infiltrates
- preauricular node often palpable and tender
- initially unilateral, often progresses to the other eye within a few days
- mainly due to adenovirus – highly contagious for up to 12 d

## Treatment
- cool compresses, topical lubrication
- usually self-limiting (7-12 d)
- proper hygiene is important to prevent transmission

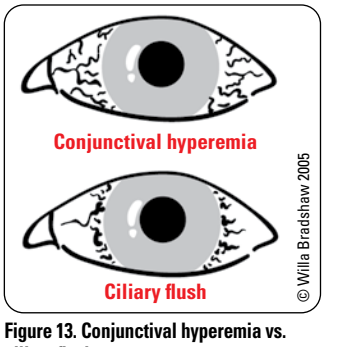



**Figure 13. Conjunctival hyperemia vs. ciliary flush**

### Bacterial Conjunctivitis
- purulent discharge, lid swelling, papillae, conjunctival injection, and chemosis
- common agents include *S. aureus, S. pneumoniae, H. influenzae* and *M. catarrhalis*
- in neonates or if sexually active must consider *N. gonorrhoeae* (invades cornea to cause keratitis)
- *C. trachomatis* is the most common cause in neonates

### Treatment
- topical broad-spectrum antibiotic, systemic antibiotics if indicated (especially in neonates and children)
- usually a self-limited course of 10-14 d if no treatment, 1-3 d with treatment

### Gonococcal and Chlamydial Conjunctivitis
- caused by *N. gonorrhoeae* and *C. trachomatis*, respectively
- affects sexually active individuals, neonates (ophthalmia neonatorum) in first 5 d of life when caused by gonorrhea (shorter incubation period) and 3-14 d of life when caused by chlamydia (longer incubation period)
- newborn prophylaxis with 0.5% erythromycin ointment- this is no longer recommended by ophthalmologists; however, it is still prescribed at some institutions
- chlamydia causes trachoma and inclusion conjunctivitis (different serotypes)

### Trachoma
- leading infectious cause of blindness in the world
- severe keratoconjunctivitis leads to corneal abrasion, ulceration, and scarring
- initially, follicles on superior palpebral conjunctiva and later palpebral scarring (Arlt's line)

### Treatment
- oral azithromycin and topical tetracycline
- IV ceftriaxone often given in the emergency department

### Inclusion Conjunctivitis
- chronic conjunctivitis with follicles and subepithelial infiltrates
- most common cause of conjunctivitis in newborns
- newborn prophylaxis with 0.5% erythromycin ointment no longer recommended

### Treatment
- oral azithromycin, tetracycline, doxycycline

- Enlarged lymph nodes suggest infectious etiology, especially viral or chlamydial conjunctivitis
- Temporal conjunctival lymphatics drain to preauricular nodes, and nasal to submandibular nodes

**Preventing Ophthalmia Neonatorum**
Paediatr Child Health 2015;20(2):93-96
The use of silver nitrate as prophylaxis for neonatal ophthalmia was instituted in the late 1800s to prevent the devastating effects of neonatal ocular infection with *Neisseria gonorrhoeae*. At that time – during the preantibiotic era – many countries made such prophylaxis mandatory by law. Today, neonatal gonococcal ophthalmia is rare in Canada, but ocular prophylaxis for this condition remains mandatory in some provinces/territories.
Silver nitrate drops are no longer available and erythromycin, the only ophthalmic antibiotic eye ointment currently available for use in newborns, is of questionable efficacy. Ocular prophylaxis is not effective in preventing chlamydial conjunctivitis. Applying medication to the eyes of newborns may result in mild eye irritation and has been perceived by some parents as interfering with mother-infant bonding. Physicians caring for newborns should advocate for rescinding mandatory ocular prophylaxis laws. More effective means of preventing ophthalmia neonatorum include screening all pregnant women for gonorrhea and chlamydia infection, and treatment and follow-up of those found to be infected. Mothers who were not screened should be tested at delivery. Infants of mothers with untreated gonococcal infection at delivery should receive ceftriaxone. Infants exposed to chlamydia at delivery should be followed closely for signs of infection.

# Sclera

- white fibrous outer protective coat of the eye, composed of irregularly distributed collagen bundles
- continuous with the cornea anteriorly and the dura of the optic nerve posteriorly
- episclera is a thin layer of vascularized tissue between the sclera and conjunctiva

# Episcleritis

### Definition
- immunologically mediated inflammation of episclera
- 1/3 bilateral; simple (80%) or nodular (20%)
- more frequent in women than men (3:1)

### Etiology
- mostly idiopathic
- associated with collagen vascular diseases, infections (herpes zoster, herpes simplex, and syphilis), inflammatory bowel disease, rosacea, and atopy

### Clinical Features
- may have discomfort and pain associated with red eye (often interpalpebral)
- sectoral or diffuse injection of radially-directed vessels, chemosis, small mobile nodules
- blanches with topical phenylephrine (constricts superficial vessels)

### Treatment
- generally self-limited, recurrent in 2/3 of cases
- topical steroid
- oral NSAIDs

To differentiate between episcleritis and scleritis, place a drop of phenylephrine 2.5% (Mydfrin®; AK-Dilate®) in the affected eye. Re-examine the vascular pattern 10-15 min later; in episcleritis the episcleral vessels should blanch with phenylephrine

# Scleritis

- usually unilateral: can be classified as anterior or posterior and diffuse, nodular, necrotizing with inflammation, or necrotizing without inflammation (scleromalacia perforans)
- anterior scleritis: pain radiating to face, may cause scleral thinning, in some cases necrotizing
- posterior scleritis: rapidly progressive blindness, may cause exudative RD
- more common in women and elderly

### Etiology
- may be a manifestation of systemic disease
- collagen vascular disease, e.g. SLE, RA, GPC, ankylosing spondylitis
- granulomatous, e.g. tuberculosis, sarcoidosis, syphilis
- metabolic, e.g. gout, thyrotoxicosis
- infectious, e.g. *S. aureus, S. pneumoniae, P. aeruginosa*, herpes zoster
- chemical or physical agents, e.g. thermal, alkali, or acid burns
- idiopathic

### Clinical Features
- severe "deep" or "boring" pain, photophobia, red eye, decreased vision
- pain is the best indicator of disease progression
- inflammation of scleral, episcleral, and conjunctival vessels
- may have anterior chamber cells and flare, corneal infiltrate, scleral thinning, scleral edema
- sclera may have a purple or "violaceous" hue (best seen in natural light), due to thinning of scleral fibres exposing the bluish-coloured uvea
- failure to blanch with topical phenylephrine

**Scleromalacia Perforans**
- Asymptomatic anterior necrotizing scleritis without inflammation
- Strongly associated with RA
- May result in scleral thinning
- Traumatic perforation can easily occur – examine eye very gently

### Treatment
- **vision threatening** – needs to be referred to ophthalmology
- life threatening- indicator of poor systemic disease control with an increased 5 yr mortality rate (not from scleritis) without treatment of underlying untreated or unrecognized autoimmune condition
- systemic NSAIDs, systemic steroid, and systemic immunomodulation
- treat underlying etiology

## Cornea

- function
  - transmission of light
  - refraction of light (2/3 of total refractive power of eye)
  - barrier against infection, foreign bodies
- transparency due to avascularity, uniform collagen structure and deturgescence (relative dehydration)
- 5 layers (anterior to posterior): epithelium, Bowman's layer, stroma, Descemet's membrane, and the endothelium (dehydrates the cornea; dysfunction leads to corneal edema). Some have argued the existence of a 6th layer, "Dua's layer", although it is debated if this is a truly unique and additional layer
- extensive sensory fibre network (V1 distribution); therefore, abrasions are very painful

**Learn the Layers of the Cornea**
**ABCDE**
**A**nterior epithelium
**B**owman's Membrane
**C**orneal Stroma
**D**ua's Layer, Descemet's Membrane
**E**ndothelium

## Foreign Body

### Definition
- foreign material in or on cornea

### Clinical Features
- patients may note pain, tearing, photophobia, foreign body sensation, and red eye
- signs include foreign body, conjunctival injection, epithelial defect that stains with fluorescein, corneal edema, and anterior chamber cells/flare
- may have associated rust ring if metallic

Foreign body behind lid may cause multiple vertical corneal epithelial abrasions due to blinking

### Complications
- abrasion, infection, ulcer, scarring, rust ring, secondary iritis

Topical analgesics should only be used to facilitate examination. They should NEVER be used as treatment for any ocular problem

### Treatment
- remove under magnification using local anesthetic and sterile needle or refer to ophthalmology for removal under magnification (depending on depth and location)
- treat as per corneal abrasion

## Corneal Abrasion

### Definition
- epithelial defect usually due to trauma (e.g. fingernails, paper, twigs), contact lens (Figure 14)

### Clinical Features (Table 7)
- pain, redness, tearing, photophobia, foreign body sensation
- de-epithelialized area stains with fluorescein dye
- pain relieved with topical anesthetic (DO NOT use for treatment- risk of corneal melt or infection)

Corneal abrasions from organic matter (e.g. twig, finger nail, etc.) have higher recurrence, even years later

### Complications
- infection, ulceration, recurrent erosion, secondary iritis

### Treatment
- topical antibiotic (drops or ointment), abrasion from organic material should be covered against *Pseudomonas*
- consider topical NSAIDs (caution due to risk of corneal melt with prolonged use), cycloplegic (relieves pain and photophobia by paralyzing ciliary muscle), patch (do not patch non-contact lens wearers as can precipitate infection)
- most abrasions clear spontaneously within 24-48 h

**Patching for Corneal Abrasion**
Cochrane Database Syst Rev 2016; 7:CD004764.
**Results:** 12 RCTs/Quasi-RCTs identified, n=1080. At 24 hours: people receiving patch were less likely to have a healed abrasion (RR 0.89, 95% CI 0.79-1.00). At 48 hours: similar effect for both groups (RR 0.97, 95% CI 0.91-1.02). At 72 hours: similar effect for both groups (RR 1.01, 95% CI 0.97-1.05)
**Summary:** Certainty of evidence is moderate to low; more research is needed with better quality trials to examine effectiveness of patching for large abrasions. Participants with patch were more likely to receive additional adjuvant treatment and took slightly longer to heal, but the difference was small and possibly clinically insignificant.

## Recurrent Erosions

### Definition
- recurrent episodes of pain, photophobia, foreign body sensation with a spontaneous corneal epithelial defect
- usually occurs upon awakening
- associated with improper adherence of epithelial cells to the underlying basement membrane

### Etiology
- previous traumatic corneal abrasion
- corneal dystrophy
- idiopathic

### Treatment
- same as corneal abrasion until re-epithelialization occurs
- topical hypertonic saline ointment at bedtime for 6-12 mo, topical lubrication
- bandage contact lens, anterior stromal puncture, superficial keratectomy with diamond burr polishing, or phototherapeutic keratectomy for chronic recurrences

## Corneal Ulcer

### Etiology
- local necrosis of corneal tissue due to infection
  - infection is usually bacterial; rarely viral, fungal, or protozoan (*Acanthamoeba*)
- secondary to corneal exposure, abrasion, foreign body, contact lens use (50% of ulcers)
- also associated with conjunctivitis, blepharitis, keratitis, vitamin A deficiency

### Clinical Features
- pain, photophobia, tearing, foreign body sensation, decreased VA (if central ulcer)
- corneal opacity that necroses and forms an excavated ulcer with infiltrative base
- overlying corneal epithelial defect that stains with fluorescein
- may develop corneal edema, conjunctival injection, anterior chamber cells/flare, hypopyon, corneal hypoesthesia (in viral keratitis)
- bacterial ulcers may have purulent discharge, viral ulcers may have watery discharge

### Complications
- decreased vision, corneal perforation, iritis, endophthalmitis

### Investigations
- Seidel test: fluorescein drop on the cornea under cobalt blue filter is used to detect leaking penetrating lesions; any aqueous leakage will dilute the green stain at site of wound

### Treatment
- urgent referral to ophthalmology
- culture prior to treatment
- topical antibiotics every hour
- must treat vigorously to avoid complications

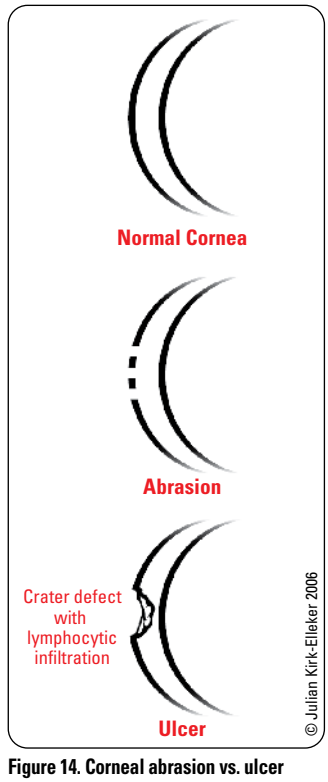


Figure 14. Corneal abrasion vs. ulcer

**Table 7. Corneal Abrasion vs. Corneal Ulcer**

| | Abrasion | Ulcer |
|---|---|---|
| **Time Course** | Acute (instantaneous) | Subacute (days) |
| **History of Trauma** | Commonly | Rare |
| **Cornea** | Clear | White, necrotic area |
| **Iris Detail** | Clear | Obscured |
| **Corneal Thickness** | Normal | May have crater defect/thinning |
| **Extent of Lesion** | Limited to epithelium | Extension into stroma |

**Abrasion vs. Ulcer on Slit-Lamp**
An abrasion appears clear while an ulcer is more opaque

# Herpes Simplex Keratitis

- usually HSV type 1 (90% of population are carriers)
- may be triggered by stress, fever, sun exposure, and immunosuppression

### Clinical Features
- pain, tearing, foreign body sensation, red eye, may have decreased vision, and eyelid edema
- corneal hypoesthesia
- classic form of HSV infectious epithelial keratitis is a dendritic (thin and branching) lesion with terminal end bulbs in epithelium that stains with fluorescein
- HSV may cause other forms of infectious epithelial keratitis, as well as stromal keratitis (which may be infectious or immune-mediated), and endotheliitis (presumably immune-mediated but possible role of live virus)

Steroid treatment for ocular disorders should only be prescribed and supervised by an ophthalmologist, as they can impair corneal healing, exacerbate herpetic keratitis, and elevate IOP

### Complications
- corneal scarring (can lead to loss of vision)
- chronic interstitial keratitis due to penetration of virus into stroma
- secondary iritis, secondary glaucoma

### Treatment
- topical antiviral such as trifluridine, or systemic antiviral such as acyclovir
- debridement of dendrite
- no steroids initially – may exacerbate condition
- ophthalmologist must exercise caution if adding topical steroids for stromal keratitis, endotheliitis or iritis, and patients covered with antiviral prophylaxis

# Herpes Zoster Ophthalmicus

### Definition
- dermatitis in the dermatomal distribution of CN V1 that is typically unilateral and respects the midline
- Hutchinson's sign: if tip of nose is involved (nasociliary branch of V1) then globe will be involved in ~75% of cases
- if no nasal involvement, eye is involved in 1/3 of patients

### Clinical Features
- pain, tearing, photophobia, red eye
- corneal edema, pseudodendrite, SPK
- corneal hypoesthesia

### Complications
- keratitis, ulceration, perforation, and scarring
- secondary iritis, secondary glaucoma, cataract
- muscle palsies (rare) due to CNS involvement
- occasionally severe post-herpetic neuralgia

### Treatment
- oral antiviral (acyclovir, valcyclovir, or famciclovir) immediately
- topical steroids, cycloplegia as indicated for immune-mediated keratitis, iritis
- erythromycin ointment if conjunctival involvement

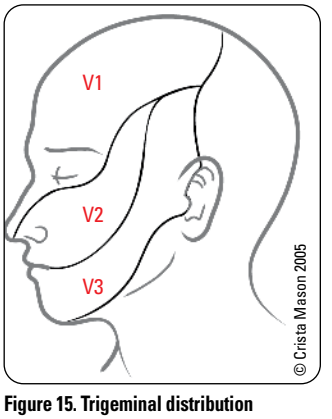


**Figure 15. Trigeminal distribution**

# Keratoconus

### Definition
- bilateral (often asymmetric) thinning and bulging (ectasia) of the cornea resulting in a conical shape
- usually sporadic but can be associated with Down syndrome, atopy, contact lens use, and vigorous eye rubbing
- associated with breaks in Descemet's membrane and Bowman's layer
- results in decreased vision from irregular astigmatism, scarring, and stromal edema

To detect keratoconus, look for bulging of the lower eyelid when the patient looks downward (Munson's sign)

### Treatment
- attempt correction with spectacles and/or rigid gas permeable contact lens
- corneal collagen cross-linking treatment to halt disease progression
- intrastromal corneal ring segments can help flatten the corneal cone
- penetrating keratoplasty or deep anterior lamellar keratoplasty (partial-thickness corneal transplant) as last resort

# Arcus Senilis

- hazy white ring in peripheral cornea, <2 mm wide, clearly separated from limbus
- common, bilateral, benign corneal degeneration due to lipid deposition, part of the aging process
- may be associated with hypercholesterolemia if age <40 yr, check lipid profile
- no associated visual symptoms, complications or treatment necessary

## Kayser-Fleischer Ring

- brown-yellow-green pigmented ring in peripheral cornea, starting inferiorly
- due to deposition of copper pigment in Descemet's membrane
- associated with Wilson's disease
- no associated symptoms or complications of ring
- treat underlying disease

# The Uveal Tract

- uveal tract (from anterior to posterior) = iris, ciliary body, choroid
- vascularized, pigmented middle layer of the eye, between the sclera and the retina

## Uveitis

- uveal inflammation which may involve one, two, or all three parts of the tract
- idiopathic or associated with autoimmune, infectious, granulomatous, and malignant causes
- should be managed by an optometrist or ophthalmologist
- anatomically classified as anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis based on primary site of inflammation

**Table 8. Anatomic Classification of Uveitis**

| | Anterior Uveitis (Iritis) | Intermediate Uveitis | Posterior Uveitis |
|---|---|---|---|
| **Location** | Inflammation of iris, usually accompanied by cyclitis (inflammation of ciliary body), both = iridocyclitis<br>Usually unilateral | The vitreous is the major site of the inflammation | Inflammation of the choroid and/or retina |
| **Etiology** | Usually idiopathic<br>Connective tissue diseases:<br>HLA-B27: reactive arthritis, ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease<br>Non-HLA-B27: juvenile idiopathic arthritis<br>Infectious: syphilis, Lyme disease, toxoplasmosis, TB, HSV, herpes zoster<br>Other: sarcoidosis, trauma, large abrasion, and postocular surgery | Mostly idiopathic, secondary causes include sarcoidosis, Lyme disease, and multiple sclerosis | Bacterial: syphilis, tuberculosis<br>Viral: herpes simplex virus, CMV in AIDS<br>Fungal: histoplasmosis, candidiasis<br>Parasitic: toxoplasmosis (most common cause), toxocara<br>Immunosuppression may predispose to any of the above infections<br>Autoimmune: Behçet's disease (triad of oral ulcers, genital ulcers, and posterior uveitis)<br>Malignancies (masquerade syndrome): metastatic lesions, malignant melanoma, lymphoma |
| **Clinical Features** | Photophobia (due to reactive spasm of inflamed iris muscle), ocular pain, tenderness of the globe, brow ache (ciliary muscle spasm), decreased VA, lacrimation<br>Ciliary flush (perilimbal conjunctival injection), miosis (spasm of sphincter muscle)<br>Anterior chamber "cells" (WBC in anterior chamber due to anterior segment inflammation) and "flare" (protein precipitates in anterior chamber secondary to inflammation), hypopyon (collection of neutrophilic exudates inferiorly in the anterior chamber)<br>Occasionally keratic precipitates (clumps of cells on corneal endothelium)<br>Iritis typically reduces IOP because ciliary body inflammation causes decreased aqueous production; however, severe iritis or iritis from herpes simplex and zoster may cause inflammatory glaucoma (trabeculitis) | Insidious onset of blurred vision, accompanied by vitreous floaters<br>Initial symptoms are usually unilateral but inflammatory changes are usually bilateral and asymmetric<br>Associated with anterior uveitis, most severe cases of secondary intermediate uveitis<br>Vitreous cells, condensations, and snowballs (vitreous aggregates of inflammatory cells)<br>Posterior segment 'snowbank' = grey-white fibrovascular plaque at the pars plana | Painless<br>Often no conjunctival or scleral injection present<br>Decreased VA<br>Floaters (debris and inflammatory cells)<br>Vitreous cells and opacities<br>Hypopyon formation |
| **Complications** | Inflammatory glaucoma<br>Posterior synechiae<br>Adhesions of posterior iris to anterior lens capsule<br>Indicated by an irregularly shaped pupil<br>If occurs 360°, can lead to angle closure glaucoma<br>Peripheral anterior synechiae (rare): adhesions of iris to cornea → secondary angle closure glaucoma<br>Cataracts<br>Band keratopathy (with chronic iritis)<br>Superficial corneal calcification keratopathy<br>Macular edema with chronic iritis | Cystoid macular edema (30% of cases), cataract, and glaucoma | Macular edema<br>Vitritis<br>Neovascularization<br>Visual field loss/scotoma |
| **Treatment** | Mydriatics: dilate pupil to prevent formation of posterior synechiae and to decrease pain from ciliary spasm<br>Steroids: topical, sub-tenon, or systemic<br>Systemic analgesia<br>If recurrent episodes, extensive medical workup may be indicated to rule out secondary causes | Systemic or sub-tenon/intravitreal steroids and immunosuppressive agents<br>Vitrectomy, cryotherapy, or laser photocoagulation to the "snowbank" | Steroids: sub-tenon, intravitreal, or systemic if indicated (e.g. threat of vision loss)<br>Vitreous biopsy if suspected masquerade/malignancy |

# Lens

- consists of an outer capsule surrounding a soft cortex and a firm inner nucleus

## Cataracts

### Definition
- any opacity of the lens, regardless of etiology
- most common cause of reversible blindness worldwide
- types: nuclear sclerosis, cortical, and posterior subcapsular

### Etiology
- acquired
  - age-related (over 90% of all cataracts)
  - cataract associated with systemic disease (may have juvenile onset)
    - DM
    - metabolic disorders (e.g. Wilson's disease, galactosemia, or homocystinuria)
    - hypocalcemia
  - traumatic (may be rosette-shaped)
  - intraocular inflammation (e.g. uveitis)
  - toxic (steroids, phenothiazines)
  - radiation
- congenital
  - high myopia
  - present with altered red reflex or leukocoria
  - treat promptly to prevent amblyopia

### Clinical Features
- gradual, painless, progressive decrease in VA
- glare, dimness, halos around lights at night, monocular diplopia
- "second sight" phenomenon: patient is more myopic than previously noted, due to increased refractive power of the lens (in nuclear sclerosis only)
  - patient may read without previously needed reading glasses
- diagnosis by slit-lamp exam
- may impair view of retina during fundoscopy

### Treatment
- medical: no role for medical management
- surgical: definitive treatment
  - indications for surgery
    - to improve visual function in patients whose vision loss leads to functional impairment
    - to aid management of other ocular disease (e.g. cataract that prevents adequate retinal exam or laser treatment of DR)
    - congenital or traumatic cataracts
  - phacoemulsification (phaco = lens)
    - most commonly used surgical technique
    - post-operative complications: RD, endophthalmitis, dislocated IOL, macular edema, glaucoma, posterior capsular opacification

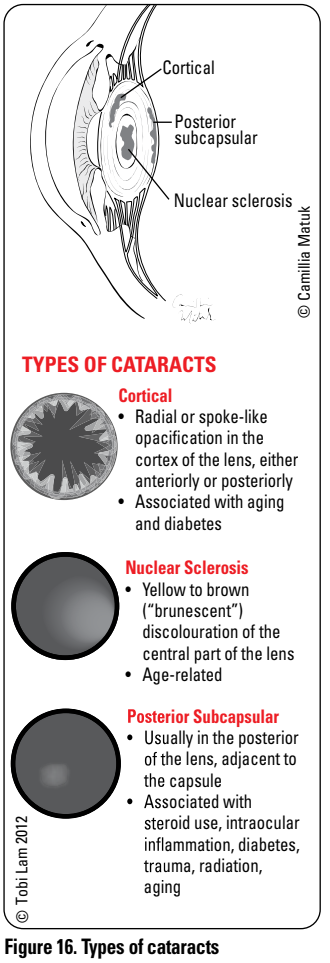


**Figure 16. Types of cataracts**

## Dislocated Lens (Ectopia Lentis)

### Etiology
- associated with Marfan's Syndrome, Ehlers-Danlos type VI, homocystinuria, syphilis, lens coloboma (congenital cleft due to failure of ocular adnexa to complete growth)
- traumatic

### Clinical Features
- decreased VA
- may get monocular diplopia
- iridodenesis (quivering of iris with movement)
- phacodonesis (observed movement of the lens)
- direct ophthalmoscopy may elicit abnormal red reflex

### Complications
- cataract, glaucoma, uveitis

### Treatment
- surgical lens replacement

# Vitreous

- clear gel (99% water plus collagen fibrils, glycosaminoglycans, and hyaluronic acid) that fills the posterior segment of eye
- normally adherent to optic disc, pars plana, and along major retinal blood vessels

## Posterior Vitreous Detachment

### Etiology
- central vitreous commonly shrinks and liquefies with age (syneresis)
- during syneresis, molecules that hold water condense causing vitreous floaters
- liquid vitreous moves between posterior vitreous gel and retina
- vitreous is peeled away and separates from the internal limiting membrane of the neurosensory retina posterior to the vitreous base

### Clinical Features
- floaters, flashes of light

### Complications
- traction at sites of firm adhesion may result in retinal tear with or without subsequent rhegmatogenous retinal detachment
- retinal tears/detachment may cause vitreous hemorrhage if bridging retinal blood vessel is torn
- complications more common in high myopes and following ocular trauma (blunt or perforating)

### Treatment
- acute onset of PVD requires a dilated fundus exam to rule out retinal tears/detachment
- no specific treatment available for floaters/flashes of light



**Weiss Ring**: formed by glial tissue around the optic disc that remains attached to the detached posterior vitreous



**Floaters**: "bugs", "cobwebs", or "spots" of vitreous condensation that move with eye position



Although most floaters are benign, new or markedly increased floaters or flashes of light require a dilated fundus exam to rule out retinal tears/detachment

## Vitreous Hemorrhage

### Definition
- bleeding into the vitreous cavity

### Etiology
- PDR
- retinal tear/detachment
- PVD
- retinal vein occlusion
- trauma

### Clinical Features
- sudden loss of VA
- may be preceded by "shower" of many floaters and/or flashes of light
- ophthalmoscopy: no red reflex if large hemorrhage, retina not visible due to blood in vitreous

### Treatment
- ultrasound (B-scan) to rule out RD
- expectant: in non-urgent cases (e.g. no RD), blood usually resorbs in 3-6 mo
- surgical: vitrectomy ± RD repair ± retinal endolaser to possible bleeding sites/vessels



Any time a vitreous or retinal hemorrhage is seen in a child, must rule out child abuse

## Endophthalmitis and Vitritis



### Definition
- intraocular infection: acute, subacute, or chronic

### Etiology
- most commonly as post-operative complication; risk following cataract surgery is <0.1%
- also due to penetrating injury to eye (risk is 3-7%), endogenous spread, and intravitreal injections
- etiology usually bacterial, may be fungal



Remember to inquire about tetanus status in post-traumatic endophthalmitis

### Clinical Features
- painful, red eye, photophobia, discharge
- severely reduced VA, lid edema, proptosis, corneal edema, anterior chamber cells/flare, hypopyon, reduced red reflex
- may have signs of a ruptured globe (severe subconjunctival hemorrhage, hyphema, decreased IOP, etc.)

### Treatment (see *Ocular Trauma*, OP40)
- **OCULAR EMERGENCY**: presenting vision best indicates prognosis
- LP or worse: admission, immediate vitrectomy, and intravitreal antibiotics to prevent loss of vision
- HM or better: vitreous tap for culture and intravitreal antibiotics
- topical fortified antibiotics

# Retina

- composed of two parts (Figure 2)
  - neurosensory retina: comprises 9 of the 10 retinal layers, including the photoreceptors and the ganglion cell layer
  - retinal pigmented epithelium layer: external to neurosensory retina
- macula: rich in cones (for colour vision); most sensitive area of retina (Figure 17)
- fovea: centre of macula; responsible for detail, fine vision, lacks retinal vessels
- optic disc: collection of retinal nerve fibre layers forming optic nerve (CNII)
- ora serrata: irregularly-shaped, anterior margin of the retina (cannot be visualized with direct ophthalmoscope)

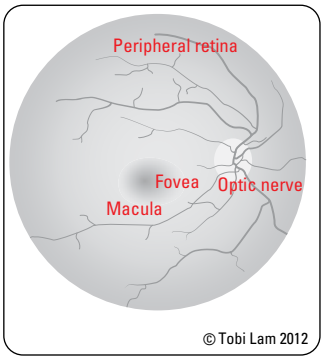



**Figure 17. Retina**

## Central/Branch Retinal Artery Occlusion

### Etiology

- occlusion of blood flow from following causes results in loss of vision due to oxygen starvation of the retinal tissues and eventual cell death
  - emboli from carotid arteries or heart (e.g. arrhythmia, endocarditis, valvular disease)
  - thrombus
  - temporal arteritis

### Clinical Features

- sudden, painless (except in GCA), severe monocular loss of vision
- RAPD
- patient may have experienced transient episodes in the past (amaurosis fugax)
- fundoscopy
  - "cherry-red spot"
  - retinal pallor
  - cotton wool spots (retinal infarcts)
  - cholesterol emboli (Hollenhorst plaques) – usually located at arteriole bifurcations

### Treatment

- **OCULAR EMERGENCY:** attempt to restore blood flow within 2 h (irreversible retinal damage if >90 min of complete CRAO)
- massage the globe (compress eye with heel of hand for 10 s, release for 10 s, repeat for 5 min) to dislodge embolus
- decrease IOP
  - topical β-blockers
  - IV acetazolamide
  - IV mannitol (draws fluid from eye)
  - drain aqueous fluid – anterior chamber paracentesis (carries risk of infection, lens puncture)
- YAG laser embolectomy
- intra-arterial or intravenous thrombolysis
- hyperbaric oxygen therapy

**Hallmark of CRAO**
"Cherry-red spot" located at centre of macula (visualization of unaffected highly vascular choroid through the thin fovea)

Treatment for a central retinal artery occlusion (CRAO) must be initiated within 2 h of symptom onset for any hope of restoring vision

The "blood and thunder" appearance on fundoscopy is very specific for CRVO

There is an 8-10% risk of developing CRVO or BRVO in other eye

**Effect of Bevacizumab vs. Aflibercept on Visual Acuity Among Patients With Macular Edema Due to Central Retinal Vein Occlusion – The SCORE2 Randomized Clinical Trial**
JAMA 2017;317(20):2072-2087
**Objective**: To investigate whether bevacizumab (used off-label) is non-inferior to aflibercept for the treatment of macular edema secondary to central retinal or hemiretinal vein occlusion
**Study**: Randomized clinical trial
**Patients**: 362 patients with macular edema due to central retinal or hemiretinal vein occlusion
**Results**: At month 6, the mean visual acuity letter score (VALS) was 69.3 (a mean increase from baseline of 18.6) in the bevacizumab group and 69.3 (a mean increase from baseline of 18.9) in the aflibercept group (P = .001 for noninferiority). Adverse events were rare but were similar between the two groups.
**Conclusion**: After 6 mo of treatment, bevacizumab was non-inferior to aflibercept with respect to visual acuity. Cost differences between the drugs has important economic implications.

## Central/Branch Retinal Vein Occlusion

### Etiology

- second most frequent "vascular" retinal disorder after DR
- exact cause is not known; possible arteriosclerotic changes in the central retinal artery transform the artery into a rigid structure and impinge upon the central retinal vein as they share a common sheath
- predisposing factors: atherosclerotic vascular disease, HTN, DM, glaucoma, hyperviscosity (e.g. sickle cell disease, polycythemia rubra vera, lymphoma, leukemia), drugs (e.g. oral contraceptive pill, diuretics)

### Clinical Features

- painless, monocular, gradual, or sudden vision loss
- ± RAPD
- fundoscopy
  - "blood and thunder" appearance
  - diffuse retinal hemorrhages, cotton wool spots, venous engorgement, swollen optic disc, macular edema
- two fairly distinct groups
  - venous stasis/non-ischemic retinopathy
    - no RAPD, VA ~20/80
    - mild hemorrhage, few cotton wool spots
    - resolves spontaneously over weeks to months
    - may regain normal vision if macula intact

**Intravitreal Aflibercet injection for Macular Edema Resulting from Central Retinal Vein Occlusion: One Year results of Phase 3 GALILEO study**
Ophthalmology 2014; 121(1) 202-8
Treatment with intravitreal aflibercept provided significant functional and anatomic benefits after 52 weeks as compared with sham. The improvement achieved after 6 monthly doses at week 24 were maintained until week 52 with prn dosing.

- hemorrhagic/ischemic retinopathy
  - usually older patient with deficient arterial supply
  - RAPD, VA ~20/200, reduced peripheral vision
  - more hemorrhages, cotton wool spots, congestion
  - poor visual prognosis

### Complications
- neovascularization of retina and iris (secondary rubeosis), leading to secondary glaucoma
- vitreous hemorrhage
- macular edema

### Treatment
- treatment available for complications of CRVO/BRVO, including retinal laser photocoagulation, anti-VEGF and/or corticosteroid injection

**Efficacy and Safety of Widely Used Treatments for Macular Edema Secondary to Retinal Vein Occlusion: A Systematic Review**
BMC Ophthalmol 2014;14:17
**Purpose**: To assess the efficacy of widely used treatments for macular edema (ME) secondary to retinal vein occlusion (RVO). ME secondary to RVO can cause vision loss due to blockage of the central retinal vein (CRVO) or a branch retinal vein (BRVO).
**Outcomes**: Mean change in best-corrected visual acuity (BCVA) from baseline and/or number of patients gaining at least 10 letters from baseline to 6 mo or equivalent time point.
**Results**: 14 unique RCTs identified. Ranibizumab 0.5 mg produced greater improvements in BCVA at 6 mo compared to sham in BRVO (mean difference 11 letters; 95% CI 7.83-14.17) and CRVO (mean difference 14 letters; 95% CI 10.51-17.69). Improvements in BCVA were also observed with dexamethasone intravitreal implant (IVT) 0.7 mg compared with sham in patients with BRVO or CRVO (mean difference 2.5 letters; 95% CI 0.7-4.3). The difference was significant with BRVO alone, but not CRVO alone. At 36 mo in a large prospective RCT, a greater proportion of patients with BRVO gained >15 letters with laser therapy versus no treatment (OR 3.16; 95% CI 1.25-8.00), whereas no difference was observed in a 9 mo endpoint smaller study. Three studies showed no benefit for laser therapy in CRVO.
**Conclusions**: Both ranibizumab and dexamethasone IVT show significant improvements over previously accepted standard of care (laser therapy) for the treatment of BRVO and CRVO.

Superotemporal retina is the most common site for horseshoe tears

# Retinal Detachment

### Definition
- cleavage in the plane between the neurosensory retina and the RPE
- three types
  - rhegmatogenous (most common)
    - caused by a tear or hole in the neurosensory retina, allowing fluid from the vitreous to pass into the subretinal space
    - tears may be caused by PVD, degenerative retinal changes, trauma, or iatrogenically
    - incidence increases with advancing age, in high myopes, and after ocular surgery/trauma
  - tractional
    - caused by vitreal, epiretinal, or subretinal membrane pulling the neurosensory retina away from the underlying RPE
    - found in conditions such as DR, RVO, sickle cell disease, ROP, and ocular trauma
  - exudative
    - caused by vascular transudation of fluid or damage to the RPE resulting in fluid accumulation in the subretinal space
    - main causes are intraocular tumour, posterior uveitis, central serous retinopathy

### Clinical Features
- sudden onset
- flashes of light
  - due to mechanical stimulation of the retinal photoreceptors
- floaters
- hazy spots in the line of vision which move with eye position
  - due to drops of blood from torn vessels bleeding into the vitreous
- curtain of blackness/peripheral field loss
  - darkness in one field of vision when the retina detaches in that area
- loss of central vision (if macula "off")
- decreased IOP (usually 4-5 mmHg lower than the other, normal eye)
- ophthalmoscopy: detached retina is grey-white from retinal edema, and loss of red reflex
- ± RAPD

### Treatment
- prophylactic: symptomatic tear (flashes or floaters) can be sealed off with laser/cryotherapy
- therapeutic:
  - rhegmatogenous
    - scleral buckle procedure
    - pneumatic retinopexy
    - vitrectomy plus injection of gas (injection of silicone oil in cases of recurrent detachment)
  - tractional
    - vitrectomy ± membrane removal/scleral buckling/injection of intraocular gas or silicone oil as necessary
  - exudative
    - management is nonsurgical; any underlying disease should be treated if possible

### Complications
- loss of vision, vitreous hemorrhage, recurrent RD
- RD is an emergency, especially if the macula is still attached (macula "on")
- prognosis for visual recovery varies inversely with the amount of time the retina is detached and whether the macula is attached or not

# Retinitis Pigmentosa

### Definition
- hereditary degenerative disease of the retina manifested by rod > cone photoreceptor degeneration and retinal atrophy
- many forms of inheritance, most commonly autosomal recessive (60%)

### Clinical Features
- night blindness, decreased peripheral vision ("tunnel vision"), decreased central vision (macular changes), glare (from posterior subcapsular cataracts, common)

### Investigations
- fundoscopy: areas of "bone-spicule" pigment clumping in mid-periphery of retina, narrowed retinal arterioles, pale optic disc
- electrophysiological tests: electroretinography (ERG) and electrooculography (EOG) assist in diagnosis

### Treatment
- gene treatments have the potential to reverse the condition; cataract extraction improves visual function; vitamin A and vitamin E supplementation can reduce progression of disease in some patients
- 3 independent clinical studies have shown safe and effective human gene therapy with rAAV2-vector for RPE65 in the treatment of Leber congenital amaurosis

**Retinitis Pigmentosa Inherited Forms**
- Autosomal recessive: most common
- Autosomal dominant: best prognosis
- X-linked: worst prognosis

**Triad of Retinitis Pigmentosa**
**APO**
**A**rteriolar narrowing
**P**erivascular bony-spicule pigmentation
**O**ptic disc pallor

## Age-Related Macular Degeneration

### Definition
- leading cause of irreversible blindness in the Western world, associated with increasing age, usually bilateral but asymmetric

### Classification
- **Non-Exudative/"Dry" (Non-Neovascular) AMD**
  - most common type of AMD (90% of cases)
  - slowly progressive loss of visual function
  - drusen: yellow-white deposits between the RPE and Bruch's membrane (area separating inner choroidal vessels from RPE)
  - geographic RPE atrophy: coalescence of RPE atrophy, clumps of focal hyperpigmentation or hypopigmentation
  - may progress to neovascular AMD

- **Exudative/"Wet" (Neovascular) AMD**
  - 10% of AMD, but 80% of AMD that results in severe vision loss
  - choroidal neovascularization: drusen predisposes to breaks in Bruch's membrane causing subsequent growth and proliferation of new, fine choroidal vessels
  - may lead to serous detachment of overlying RPE and retina, hemorrhage, and lipid precipitates into the subretinal space
  - can also lead to an elevated subretinal mass due to fibrous metaplasia of subretinal fibrovascular proliferation progresses to disciform scarring and severe central vision loss

### Risk Factors
- female
- increasing age
- family history
- smoking
- Caucasian race
- blue irides

### Clinical Features
- variable degree of progressive central vision loss
- metamorphopsia (distorted vision characterized by straight parallel lines appearing convergent or wavy) due to macular edema

### Investigations
- Amsler grid: held at normal reading distance with glasses on, assesses macular function
- Fluorescein angiography: assess type and location of choroidal neovascularization – pathologic new vessels leak dye
- OCT retinal imaging: assess the amount of intraretinal and subretinal exudation

### Treatment
- non-neovascular "dry" AMD
  - monitor, Amsler grid allows patients to check for metamorphopsia
  - low vision aids (e.g. magnifiers, closed-circuit television)
  - anti-oxidants, green leafy vegetables
  - sunglasses/visors
  - see Age-related Eye Disease Study 2 (AREDS2) in sidebar
- neovascular "wet" AMD
  - see *Common Medications*, OP42
  - intravitreal injection of anti-VEGF
    - pegaptanib (Macugen®), ranibizumab (Lucentis®), bevacizumab (Avastin®), aflibercept (Eylea®) (see *VEGF Inhibitors*, OP43)
  - no definitive treatment for disciform scarring
  - photodynamic therapy with verteporfin (Visudyne®)
    - IV injection of verteporfin, followed by low-intensity laser to area of choroidal neovascularization

**Age-Related Eye Disease Study 2 (AREDS2) Lutein + zeaxanthin and omega-3 fatty acids for AMD: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial.**
Jama 2013; 309(19):2005-15
The original AREDS formulation contains vitamin C, E and β-carotene, zinc and copper; reduced risk of progression to advanced AMD by 2%. Addition of lutein+zeaxanthin, DHA/EPA, or both to the AREDS formulation in primary analyses didn't reduce risk of progression to advance AMD. However, because of the potential increased incidence of lung cancer in former smokers, lutein+zeaxanthin could be an appropriate carotenoid substitute in the AREDS formulation.

# Glaucoma

## Definition
- progressive, pressure-sensitive, optic neuropathy involving characteristic structural changes to optic nerve head with associated visual field changes
- commonly associated with high IOP, but not required for diagnosis

## Background
- aqueous is produced by the ciliary body and drains into the episcleral veins via the trabecular meshwork and the Canal of Schlemm
- an isolated increase in IOP is termed ocular hypertension (OHT) - should be followed for increased risk of developing glaucoma
- pressures >21 mmHg increase the risk of developing glaucoma
- loss of peripheral vision most commonly precedes central vision loss
- structural changes commonly precede functional changes

## Investigations
- VA testing
- slit-lamp exam to assess anterior chamber depth; gonioscopy to assess angle patency
- ophthalmoscopy to assess the disc features
- tonometry to measure IOP
- visual field testing
- pachymetry to measure corneal thickness
- OCT of the nerve fibre layer (NFL) at the optic nerve to monitor for loss of NFL
- follow-up includes optic disc examination, IOP measurement, OCT of the optic nerve and visual field testing to monitor course of disease

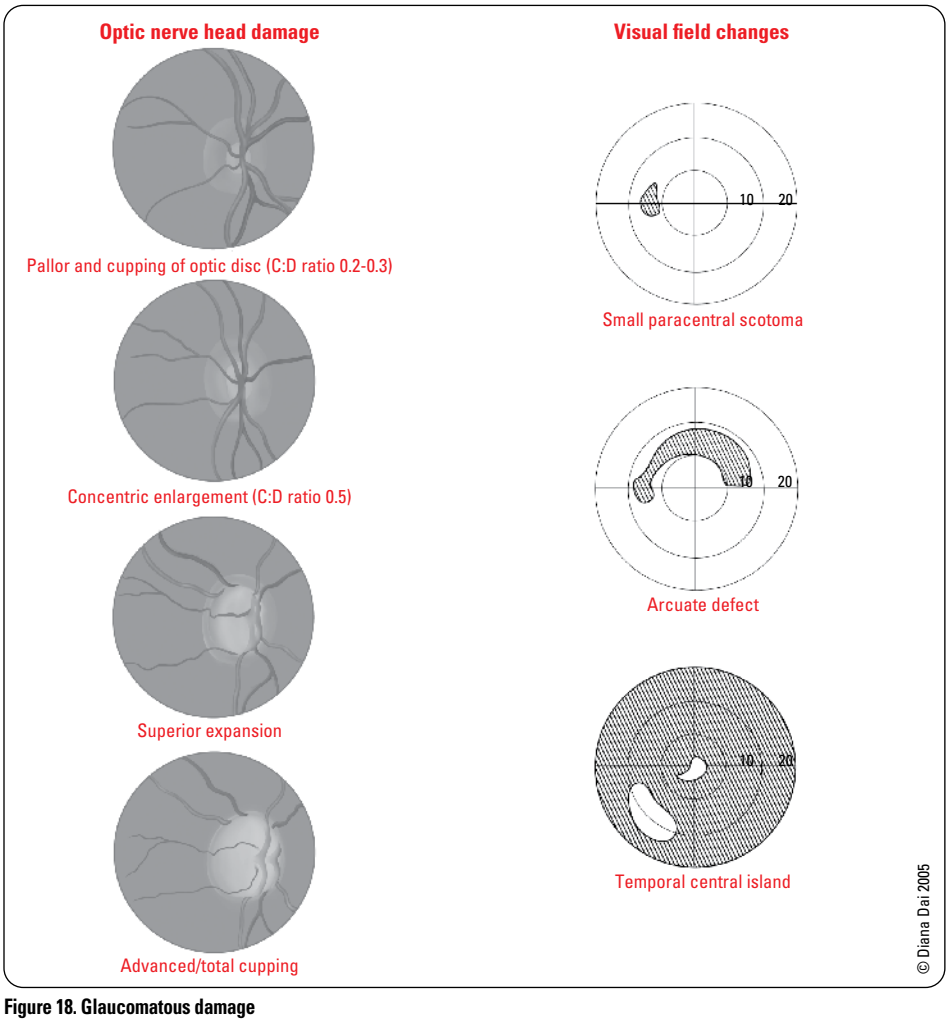
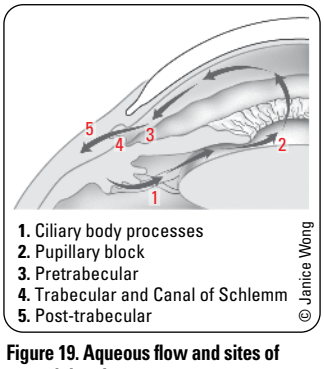



**Figure 18. Glaucomatous damage**

**Ten Year Follow-Up of Age-Related Macular Degeneration in the Age-Related Eye Disease Study: AREDS Report No. 36**
JAMA Ophthalmol 2014;132(3):272-7
**Study**: Randomized clinical trial.
**Objective**: To describe 10 yr progression rates to intermediate or advanced AMD.
**Patients**: Age-related eye disease study (AREDS) participants were observed for an additional 5 yr after RCT completion. Participants aged 55-80 yr with no AMD or AMD of varying severity (n = 4757) were followed up in the AREDS trial for a median duration of 6.5 yr. When the trial ended, 3549 of the 4203 surviving participants were followed for 5 additional yr.
**Intervention**: Treatment with antioxidant vitamins and minerals.
**Main Outcome**: Development of varying stages of AMD and changes in visual acuity.
**Results**: The risk of progression to advanced AMD increased with increasing age (p=0.01) and severity of drusen. Women (p=0.005) and current smokers (p<0.001) were at increased risk of neovascular AMD. In the oldest participants with the most severe AMD status at baseline, the risks of developing neovascular AMD and central geographic atrophy by 10 yr were 48.1% and 26.0%, respectively. Similarly, rates of progression to large drusen increased with increasing severity of drusen at baseline, with 70.9% of participants with bilateral medium drusen progressing to large drusen and 13.8% to advanced AMD in 10 yr. Median visual acuity at 10 yr in eyes that had large drusen at baseline but never developed advanced AMD was 20/25; eyes that developed advanced AMD had a median visual acuity of 20/200.
**Conclusion**: The natural history of AMD demonstrates relentless loss of vision in persons who developed advanced AMD.

Average IOP: 15 ± 3 mmHg
Normal C:D : ≤0.4
Suspect glaucoma if C:D ratio >0.6, C:D ratio differs between eyes by >0.2, or cup approaches disc margin




**1.** Ciliary body processes
**2.** Pupillary block
**3.** Pretrabecular
**4.** Trabecular and Canal of Schlemm
**5.** Post-trabecular

**Figure 19. Aqueous flow and sites of potential resistance**

# Primary Open-Angle Glaucoma

## Definition
- most common form, >95% of all glaucoma cases
- unobstructed open-angle, resistance is within the trabecular meshwork
- insidious and asymptomatic, screening is critical for early detection

## Major Risk Factors
- ocular hypertension (IOP >21 mmHg)
- age: prevalence at 40 yr is 1-2% and at 80 yr is 10%
- ethnicity: African descent
- familial (2-3x increased risk); polygenic
- thin central cornea (OHTS trial)

## Minor Risk Factors
- myopia
- HTN
- DM
- hyperthyroidism (Graves' disease)
- chronic topical ophthalmic steroid use in steroid responders – yearly eye exams recommended if >4 wk of steroid use
- previous ocular trauma
- anemia/hemodynamic crisis (ask about blood transfusions in past)

## Clinical Features
- asymptomatic initially
- insidious, painless, gradual rise in IOP due to restriction of aqueous outflow
- bilateral, but usually asymmetric
- earliest signs are optic disc changes
  - increased C:D ratio (vertical C:D >0.6)
  - significant C:D asymmetry between eyes (>0.2 difference)
  - thinning, notching of the neuroretinal rim
  - flame shaped disc hemorrhage
  - 360° of peripapillary atrophy
  - nerve fibre layer defect
  - large vessels become nasally displaced
- visual field loss
- slow, progressive, irreversible loss of peripheral vision
- paracentral defects, arcuate scotoma, and nasal step are characteristics (Figure 18)
- late loss of central vision if untreated

## Treatment
- medical treatment: decrease IOP by increasing the drainage and/or decreasing the production of aqueous (see *Glaucoma Medications*, Table 14, OP43)
  - increase aqueous outflow
    - topical prostaglandin analogues
    - topical α-adrenergics
    - topical cholinergics
  - decrease aqueous production
    - topical β-blockers
    - topical and oral carbonic anhydrase inhibitors
    - topical α-adrenergics
- laser trabeculoplasty, cyclophotocoagulation in order to achieve selective destruction of ciliary body (for refractory cases)
- trabeculectomy: creation of a new outflow tract from anterior chamber to under the conjunctiva forming a bleb
- minimally invasive glaucoma surgery (MIGS): implantation of IOP lowering drainage devices (e.g. iStent), high safety profile and generally for patients with mild to moderate glaucoma
- tube shunt: for advanced stages of glaucoma
- serial optic nerve head examinations, IOP measurements, OCT of optic nerve and visual field testing to monitor disease course

**Risk Factors for POAG**
**A FIAT**
**A**ge
**F**amily history
**I**OP
**A**frican descent
**T**hin cornea

**Open- and Closed-Angle Glaucoma**

| POAG | PACG |
|---|---|
| • Common (95%) | • Rare (5%) |
| • Chronic course | • Acute onset |
| • Painless eye without redness | • Painful red eye |
| • Moderately ↑ IOP | • Extremely ↑ IOP |
| • Normal cornea and pupil | • Hazy cornea |
| • No N/V | • Mid-dilated pupil unreactive to light |
| • No halos around light | • ± N/V, abdominal pain |
| | • Halos around light |

Elevated IOP is the only modifiable risk factor that has been proven to prevent progression of glaucoma. Treating patients with ocular hypertension but no signs of glaucoma has also shown to reduce the risk of developing glaucoma

**The Ocular Hypertension Treatment Study**
Arch Ophthalmol-Chic 2002;120:701-713
**Study**: Randomized clinical trial.
**Patients**: 1636 patients with no evidence of glaucomatous damage, aged 40-80 yr, and with IOP between 24-32 mmHg in one eye and between 21-32 mmHg in the other eye.
**Intervention**: Randomized to observation or treatment with commercially available topical ocular hypotensive medication.
**Main Outcome**: Development of visual field abnormality or optic disc deterioration attributed to POAG.
**Results**: Mean reduction in IOP in the medication group was 22.5% ± 9.9% vs. 4.0% ± 11.6% in the observation group. At 5 yr, the probability of developing POAG was 4.4% in the medication group and 9.5% in the observation group ($p<0.0001$).
**Conclusions**: Topical ocular hypotensive medication was effective in delaying or preventing the onset of POAG in individuals with elevated IOP.

# Normal Tension Glaucoma

## Definition
- POAG with IOP in normal range
- often found in women >60 yr, but may occur earlier
- associated with migraines, peripheral vasospasm, systemic nocturnal hypotension, sleep apnea
- damage to optic nerve may be due to vascular insufficiency

## Treatment
- treat reversible causes

# Secondary Open-Angle Glaucoma

## Etiology
- increased IOP secondary to ocular/systemic disorders that obstruct the trabecular meshwork including:
  - steroid-induced glaucoma, traumatic glaucoma, pigmentary dispersion syndrome, pseudoexfoliation syndrome

**Rule of Fours**
1/4 of general population using topical steroid for 4 wk, 4x/d will develop an increase in IOP

# Primary Angle-Closure Glaucoma

## Definition
- 5% of all glaucoma cases
- peripheral iris bows forward obstructing aqueous access to the trabecular meshwork
- sudden forward shift of the lens-iris diaphragm causes pupillary block and results in impaired drainage, leading to a sudden rise in IOP

## Risk Factors
- hyperopia: small eye, big lens – large lens crowds the angle
- age >70 yr
- female
- family history
- more common in people of Asian and Inuit descent
- mature cataracts
- shallow anterior chamber
- pupil dilation (topical and systemic anticholinergics, stress, darkness)

## Clinical Features
- red, painful eye = **RED FLAG**
- unilateral, but other eye at increased risk
- decreased visual acuity, vision acutely blurred from corneal edema
- halos around lights
- nausea and vomiting, abdominal pain
- fixed, mid-dilated pupil
- marked increase in IOP; may be noticeable even to palpation (>40 mmHg)
- shallow anterior chamber ± cells in anterior chamber

## Complications
- irreversible loss of vision within hours to days if untreated
- permanent peripheral anterior synechiae, resulting in permanent angle closure

## Treatment
- **OCULAR EMERGENCY:** refer to ophthalmologist for acute angle-closure glaucoma
- medical treatment (see *Glaucoma Medications*, Table 14, OP43)
  - aqueous suppressants and hyperosmotic agents
  - miotic drops (pilocarpine) to reverse pupillary block
  - multiple topical IOP-lowering agents
  - hypserosmotic agents such as oral glycerine, or IV mannitol
- laser iridotomy is definitive

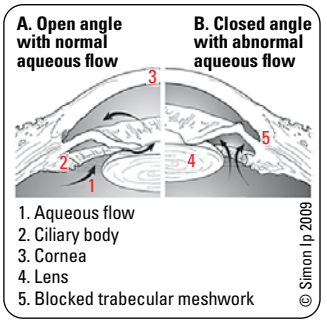



**Figure 20. Normal open-angle vs. angle-closure glaucoma**

**Angle-Closure Glaucoma**
**BACH**
Tx with miotics and β-**b**lockers
**A**drenergics
**C**holinergics
**H**yperosmotic agents

**Collaborative Normal Tension Glaucoma Study**
*Curr Opin Ophthalmol* 2003;14:86-90
Treatment aimed at lowering IOP by 30% in patients with normal tension glaucoma tends to reduce the rate of visual field loss. Due to variability in disease progression and a significant group that shows no visual field loss at 5 yr despite no treatment, further studies are needed to delineate which subgroups may benefit most from treatment.

# Secondary Angle-Closure Glaucoma

## Uveitis
- inflamed iris adheres to lens (posterior synechiae)

## Neovascular Glaucoma
- abnormal blood vessels develop on surface of iris (rubeosis iridis), in the angle, and within the trabecular meshwork
- due to retinal ischemia associated with PDR or CRVO
- treatment with laser therapy to retina reduces neovascular stimulus to iris and angle vessels

# Pupils

- pupil size is determined by the balance between the sphincter muscle and the dilator muscle
- sphincter muscle is innervated by the parasympathetic nervous system carried by CN III
- dilator muscle is innervated by the sympathetic nervous system (SNS)
  - first-order neuron = hypothalamus → brainstem → spinal cord
  - second-order/preganglionic neuron = spinal cord → sympathetic trunk via internal carotid artery → superior cervical ganglion in neck
  - third-order/postganglionic fibres originate in the superior cervical ganglion, neurotransmitter is norepinephrine
    - as a diagnostic test, 4-10% cocaine prevents the reuptake of norepinephrine, and will cause dilation of normal pupil, but not one with loss of sympathetic innervation (Horner's Syndrome)
- see Neurology, Figure 8, N8



**5 Targets of Retinal Signals**
- Pretectal nucleus (pupillary reflex/eye movements)
- Lateral geniculate body of thalamus
- Superior colliculus (eye movements)
- Suprachiasmatic nucleus (optokinetic)
- Accessory optic system (circadian rhythm)

# Pupillary Light Reflex

- light shone directly into eye travels along optic nerve (CN II, afferent limb) → optic tracts → bilateral midbrain
- impulses enter bilaterally in midbrain via pretectal area and Edinger-Westphal nuclei
- nerve impulses then travel down CN III (efferent limb) bilaterally to reach the ciliary ganglia, and finally to the iris sphincter muscle, which results in the direct and consensual light reflexes

α1 – Pupillary dilator muscle contraction (mydriasis)
β2 – Ciliary muscle relaxation (non-accommodation); increased aqueous humour production
M3 – Pupillary sphincter contraction (miosis); increased ciliary muscle contraction (Accommodation)

# Pupil Abnormalities



### Denervation Hypersensitivity
- when postganglionic fibres are damaged, the under-stimulated end-organ attempts to compensate by developing an increase of neuroreceptors and becomes hypersensitive
- postganglionic parasympathetic lesions (i.e. Adie's pupil)
  - pupil will constrict with 0.125% pilocarpine (cholinergic agonist), normal pupil will not
- postganglionic sympathetic lesions (this test is used to differentiate between pre- and post-ganglionic lesions in Horner's syndrome)
  - pupil will dilate with 0.125% epinephrine, normal pupil will not

### Local Disorders of Iris
- posterior synechiae (adhesions between iris and lens) due to iritis can present as an abnormally shaped pupil
- ischemic damage (e.g. post-acute angle-closure glaucoma) usually occurs at 3 and 9 o'clock positions resulting in a vertically oval pupil that reacts poorly to light
- trauma (e.g. post-intraocular surgery)

### Anisocoria
- unequal pupil size
- idiopathic/physiologic anisocoria
  - 20% of population
  - round, regular, <1 mm difference
  - pupils reactive to light and accommodation
  - responds normally to mydiatrics/miotics
  - post eye surgery, or extensive retinal laser treatment
- see Table 9 for other causes of anisocoria

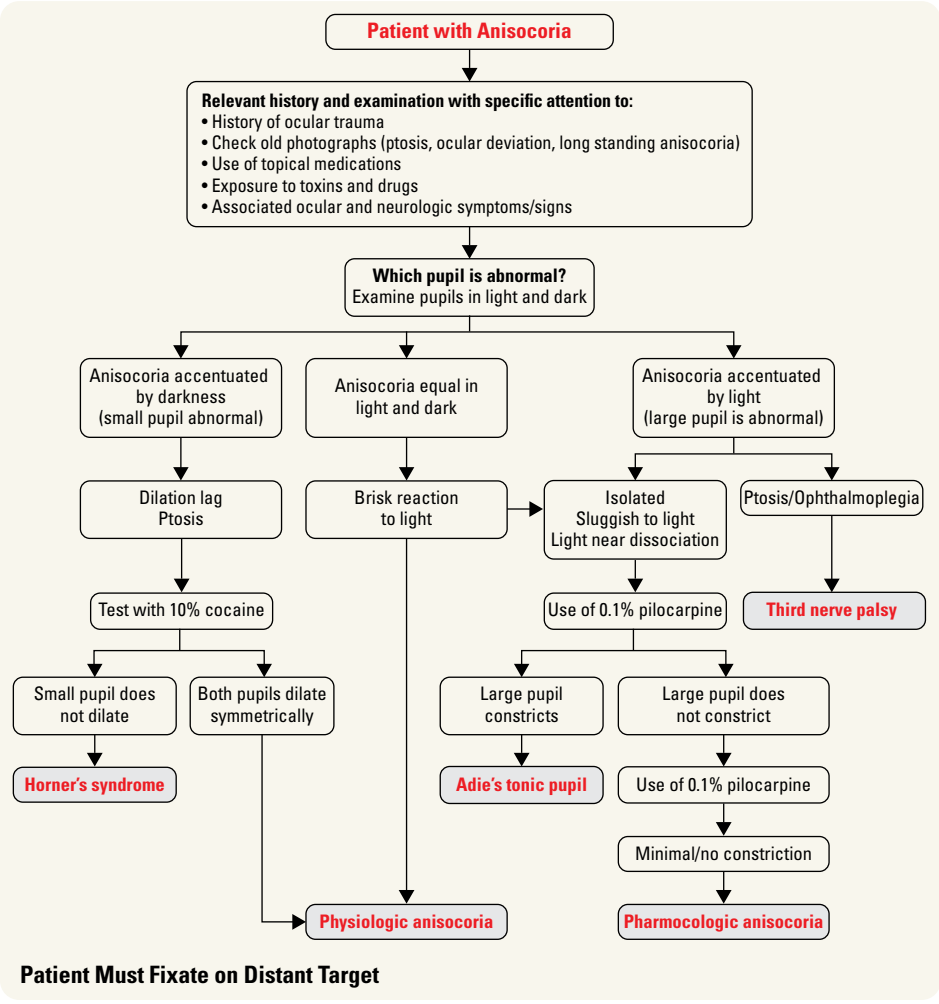



**Figure 21. Approach to anisocoria**

Reproduced with permission from: Kedar S, Biousse V, Newman NJ. Approach to the patient with anisocoria. In: UpToDate, Rose, BD (editor), UpToDate, Waltham, MA, 2011. Copyright 2011 UpToDate, Inc. For more information visit www.uptodate.com.

**Table 9. Summary of Conditions Causing Anisocoria**

| | Features | Site of Lesion | Light and Accommodation | Anisocoria | Mydriatics/ Miotics | Effect of Pilocarpine |
|---|---|---|---|---|---|---|
| **ABNORMAL MIOTIC PUPIL (impaired pupillary dilation)** | | | | | | |
| **Argyll-Robertson Pupil** | Irregular, usually bilateral | Midbrain | Poor in light; better to accommodation | | Dilates/ Constricts | |
| **Horner's Syndrome** | Round, unilateral, ptosis, anhydrosis, pseudoenophthalmos | Sympathetic system | Both brisk | Greater in dark | Dilates/ Constricts | |
| **ABNORMAL MYDRIATIC PUPIL (impaired pupillary constriction)** | | | | | | |
| **Adie's Tonic Pupil** | Irregular, larger in bright light | Ciliary ganglion | Poor in light, better to accommodation | Greater in light | Dilates/ Constricts | Constricts (hypersensitivity to dilute pilocarpine) |
| **CN III Palsy** | Round | Superficial CN III | ± fixed (acutely) at 7-9 mm | Greater in light | Dilates/ Constricts | Constricts |
| **Mydriatic Pupil** | Round, uni- or bilateral | Iris sphincter | Fixed at 7-8 mm | Greater in light | No effect | Will not constrict |

# Dilated Pupil (Mydriasis)

### Sympathetic Stimulation
- fight or flight response
- mydriatic drugs: epinephrine, dipivefrin (Propine®), phenylephrine

### Parasympathetic Under-stimulation
- cycloplegics/mydriatics: atropine, tropicamide, cyclopentolate (parasympatholytic)
- CN III palsy
  - eye deviated down and out with ptosis present
  - etiology includes stroke, neoplasm, aneurysm, acute rise in ICP, DM (may spare pupil), trauma
  - both mydriatics and CN III palsy cause pupil dilation; however, pupils in CN III palsy will constrict briskly to pilocarpine, while pupils dilated from mydriatics will not

### Acute Angle-Closure Glaucoma
- fixed, mid-dilated pupil

### Adie's Tonic Pupil
- 80% unilateral, F>M
- pupil is tonic or reacts poorly to light (both direct and consensual) but constricts with accommodation
- caused by benign lesion in ciliary ganglion; results in denervation hypersensitivity of parasympathetically innervated constrictor muscle
  - dilute (0.125%) solution of pilocarpine will constrict tonic pupil but have no effect on normal pupil
- long-standing Adie's pupils are smaller than unaffected eye

### Trauma
- damage to iris sphincter from blunt or penetrating trauma
- iris transillumination defects may be apparent using ophthalmoscope or slit-lamp
- pupil may be dilated (traumatic mydriasis) or irregularly shaped from tiny sphincter ruptures

# Constricted Pupil (Miosis)

### Senile Miosis
- decreased sympathetic stimulation with age

### Parasympathetic Stimulation
- local or systemic medications such as:
  - cholinergic agents: pilocarpine, carbachol
  - cholinesterase inhibitor: phospholine iodide
  - opiates, barbiturates

### Horner's Syndrome
- lesion in sympathetic pathway
- difference in pupil size greater in dim light, due to decreased innervation of adrenergics to iris dilator muscle
- associated with ptosis and anhydrosis of ipsilateral face/neck
- application of cocaine 4-10% (blocks reuptake of norepinephrine) to eye does not result in pupil dilation (vs. physiologic anisocoria), therefore confirms diagnosis
- hydroxyamphetamine 1% (stimulates norepinephrine release) will dilate pupil if central or preganglionic lesion, not postganglionic lesion
- now more commonly, topical apraclonidine 0.5%
- postganglionic lesions result in denervation hypersensitivity, which will cause pupil to dilate with 0.125% epinephrine, whereas normal pupil will not
- causes: carotid or subclavian aneurysm, brainstem infarct, demyelinating disease, cervical or mediastinal tumour, Pancoast tumour, goitre, cervical lymphadenopathy, surgical sympathectomy, Lyme disease, cervical ribs, tabes dorsalis, cervical vertebral fractures

### Iritis
- miotic pupil initially
- can become irregularly shaped pupil due to posterior synechiae
- later stages non-reactive to light

### Argyll-Robertson Pupil
- both pupils irregular and <3 mm in diameter, ± ptosis
- does not respond to light stimulation
- responds to accommodation (light-near dissociation)
- suggestive of neurosyphilis or other conditions (DM, encephalitis, MS, chronic alcoholism, CNS degenerative diseases)

### Other Causes
- optic neuritis, retinal lesions

CN III palsy with pupillary involvement may be associated with a posterior communicating artery aneurysm

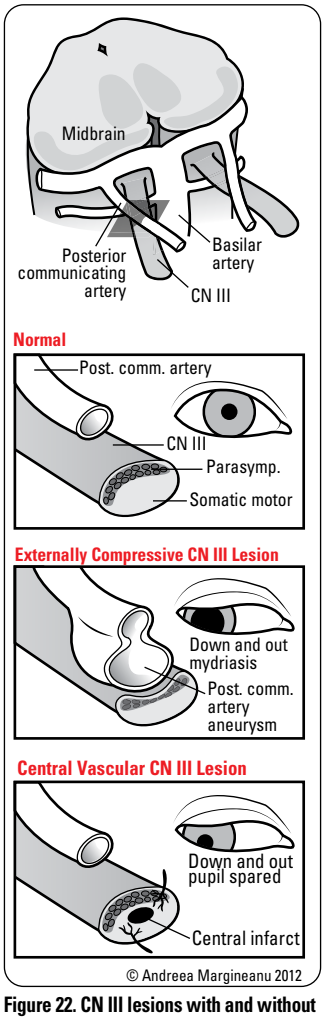



**Figure 22. CN III lesions with and without mydriasis**

**Horner's MAP**
**M**iosis
**A**nhydrosis
**P**tosis

# Relative Afferent Pupillary Defect

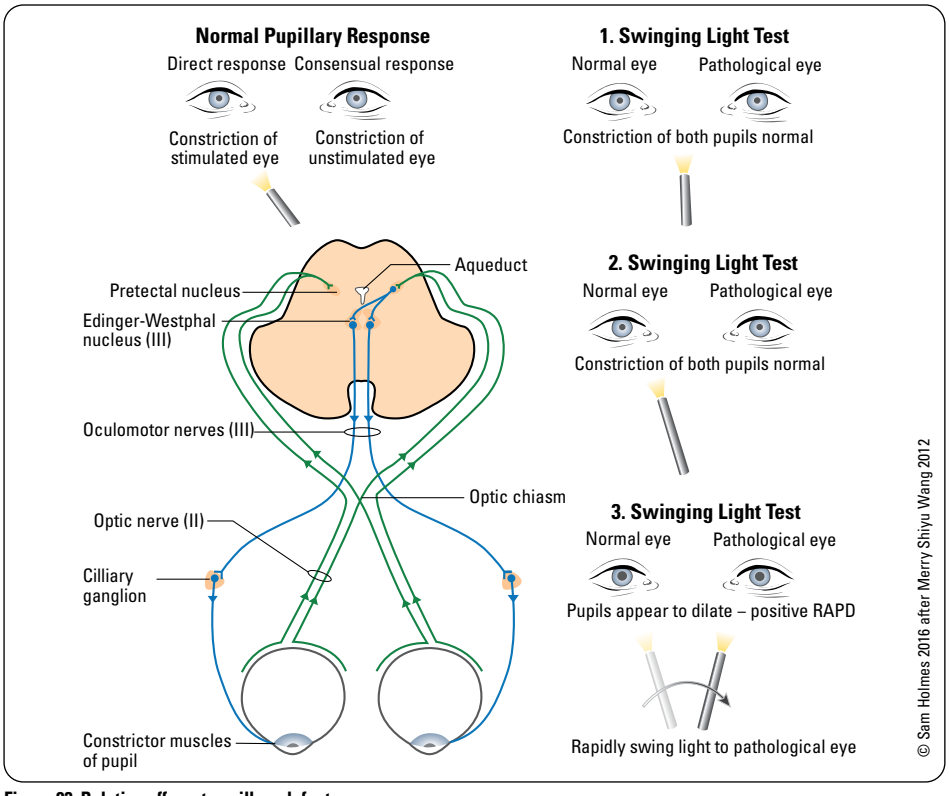



**Figure 23. Relative afferent pupillary defect**

- also known as Marcus Gunn pupil
- impairment of direct pupillary response to light caused by a lesion in visual afferent (sensory) pathway, anterior to optic chiasm
- differential diagnosis: large RD, BRAO, CRAO, CRVO, advanced glaucoma, optic nerve compression, **optic neuritis** (most common)
- does not occur with media opacity (e.g. corneal edema, cataracts)
- pupil reacts poorly to light and better to accommodation
- test: swinging flashlight
  - if light is shone in the affected eye, direct and consensual response to light is decreased
  - if light is shone in the unaffected eye, direct and consensual response to light is normal
  - if the light is moved quickly from the unaffected eye to the affected eye, "paradoxical" dilation of both pupils occurs
  - observe red reflex, especially in patients with dark irides
- if the defect is bilateral there is no RAPD, as dilation is measured relative to the other eye

Cataracts never produce a RAPD

It is possible to have RAPD and normal vision at the same time, e.g. in damaged superior colliculus caused by thalamic hemorrhage

Differentiate RAPD from physiologic pupillary athetosis ("hippus"), which is rapid, rhythmic fluctuations of the pupil, with equal amplitude in both eyes

# Malignancies

- uncommon site for 1° malignancies
- see *Retinoblastoma*, OP38

# Lid Carcinoma

## Etiology

- basal cell carcinoma (rodent ulcer) (90%)
  - spread via local invasion, rarely metastasizes
  - ulcerated centre, indurated base with pearly rolled edges, telangiectasia
- squamous cell carcinoma (<5%)
  - spread via local invasion, may also spread to nodes and metastasize
  - ulceration, keratosis of lesion
- sebaceous cell carcinoma (1-5%)
  - often masquerades as chronic blepharitis or recurrent chalazion
  - highly invasive, metastasizes
- other: Kaposi's sarcoma, malignant melanoma, Merkel cell tumour, metastatic tumour

### Treatment
- incisional or excisional biopsies
- may require cryotherapy, radiotherapy, chemotherapy, immunotherapy
- surgical reconstruction

## Uveal Melanoma

### Etiology
- most common 1° intraocular malignancy in adults
- more prevalent in Caucasians
- arise from uveal tract, 90% choroidal melanoma
- hepatic metastases predominate

### Clinical Features
- classic appearance of a pigmented dome-shaped mass extending from the ciliary body or the choroid
- diagnosis necessitates expertise of an ophthalmologist/ocular oncologist

### Treatment
- investigations: ocular ultrasound, fluorescent angiogram, OCT, and systemic cancer investigations
- depending on the size of the tumour, either radiotherapy (brachytherapy vs external beam), or enucleation

**To Find Small Ocular Melanoma**

**TFSOM**
**T** – **T**hickness >2 mm
**F** – Subretinal **F**luid
**S** – **S**ymptoms – vision changes
**O** – **O**range pigment
**M** – **M**argin within 3 mm of optic disc

## Metastases

- most common intraocular malignancy in adults
- most commonly from breast and lung in adults, neuroblastoma in children
- usually infiltrate the choroid, but may also affect the optic nerve or extraocular muscles
- may present with decreased or distorted vision, irregularly shaped pupil, iritis, hyphema

### Treatment
- local radiation, chemotherapy
- enucleation if blind, painful eye

# Ocular Manifestations of Systemic Disease

## HIV/AIDS

- up to 75% of patients with AIDS have ocular manifestations

### External Ocular Signs
- Kaposi's sarcoma
  - secondary to human herpes virus 8 (HHV-8), causes bright red conjunctival lesion and subconjunctival hemorrhage
  - differential diagnosis: subconjunctival hemorrhage (non-clearing), hemangioma
- multiple molluscum contagiosum
- herpes simplex/zoster keratitis

### Retina
- HIV retinopathy (most common)
  - cotton wool spots in >50% of HIV patients
  - intraretinal hemorrhage
- CMV retinitis
  - ocular opportunistic infection that develops when severely immunocompromised (CD4 count ≤50)
  - a necrotizing retinitis, with retinal hemorrhages and vasculitis, "brushfire" or "pizza pie" appearance
  - presents with scotoma (macular involvement and RD), blurred vision, and floaters
  - untreated infection will progress to other eye in 4-6 wk
  - treatment: virostatic agents (e.g. ganciclovir or foscarnet) via IV or intravitreal injection
- necrotizing retinitis
  - from herpes simplex virus, herpes zoster, toxoplasmosisdisseminated choroiditis
  - *Pneumocystis carinii* and *Mycobacterium avium intracellulare* can present with choroiditis
  - *Candida* can present as retinitis and vitritis

## Other Systemic Infections

- herpes zoster
  - see *Herpes Zoster*, OP18
- candidal endophthalmitis
  - fluffy, white-yellow, superficial retinal infiltrate that may eventually result in vitritis
  - may present with inflammation of the anterior chamber
  - treatment: systemic amphotericin B, oral fluconazole

- toxoplasmosis
  - focal, grey-yellow-white, chorioretinal lesions with surrounding vasculitis and vitreous infiltration (vitreous cells)
  - can be congenital (transplacental) or acquired (caused by *Toxoplasma gondii* protozoa transmitted through raw meat and cat feces)
  - congenital form more often causes visual impairment (more likely to involve the macula)
  - treatment: pyrimethamine, sulfonamide, folinic acid, or clindamycin. Consider adding steroids if severe inflammation (vitritis, macular or optic nerve involvement)

# Diabetes Mellitus

- most common cause of blindness in young people in North America
- loss of vision due to:
  - progressive microangiopathy leading to macular edema
  - progressive DR → neovascularization → traction → RD and vitreous hemorrhage
  - rubeosis iridis (neovascularization of the iris) leading to neovascular glaucoma (poor prognosis)
  - macular ischemia

## DIABETIC RETINOPATHY

### Background
- altered vascular permeability (loss of pericytes and thickening of basement membrane causing breakdown of blood-retinal barrier)
- predisposition to retinal vessel obstruction (CRAO, CRVO, and BRVO)

### Classification
- non-proliferative: increased vascular permeability and retinal ischemia
  - hard exudates (lipid deposits)
  - dot and blot hemorrhages
  - microaneurysms
  - retinal edema
- advanced non-proliferative (or pre-proliferative)
  - non-proliferative findings plus:
    - venous beading (in ≥2 of 4 retinal quadrants)
    - intraretinal microvascular anomalies (IRMA) in 1 of 4 retinal quadrants
      - IRMA: dilated, leaky collateral vessels within the retina
    - nerve fibre layer (NFL) infarcts (i.e. cotton-wool spots)
- proliferative
  - 5% of patients with DM will reach this stage
  - neovascularization of iris, disc, retina
    - neovascularization of iris (rubeosis iridis) can lead to neovascular glaucoma
    - vitreous hemorrhage, bleeding from fragile new vessels, fibrous tissue can contract causing tractional RD
  - may remain asymptomatic in early stage
  - high risk of severe vision loss secondary to vitreous hemorrhage, RD

### Screening Guidelines for Diabetic Retinopathy
- type 1 DM
  - screen for retinopathy beginning annually 5 yr after disease onset
  - annual screening indicated for all patients over 12 yr and/or entering puberty
- type 2 DM
  - initial examination at time of diagnosis, then annually
- pregnancy
  - ocular exam in 1st trimester, close follow-up throughout as pregnancy can exacerbate DR
  - patients with gestational diabetes are not at risk of having DR

### Treatment
- 1° prevention: tight control of blood glucose, blood pressure, serum lipid levels, kidney function, and macrovascular complications (Diabetic Control and Complications Trial (DCCT))
- 2° prevention: laser photocoagulation
- 3° prevention:
  - pan-retinal laser photocoagulation (PRP) for PDR: reduces neovascularization, hence reducing the angiogenic stimulus from ischemic retina by decreasing retinal metabolic demand → reduces risk of blindness
  - intravitreal injection of corticosteroid or anti-VEGF for fovea-involved diabetic macular edema
  - macular photocoagulation laser for clinically significant macular edema (when not involving centre of macula)
  - vitrectomy for non-clearing vitreous hemorrhage and tractional RD in PDR
    - vitrectomy before vitreous hemorrhage does not improve the visual prognosis

### Lens Changes
- earlier onset of senile nuclear sclerotic and cortical cataracts
- may get hyperglycemic cataract due to sorbitol accumulation (rare)
- changes in blood glucose levels (poor control) can suddenly cause refractive changes by 3-4 diopters



Macular edema is the most common cause of visual loss in patients with background DR



**Anti-vascular endothelial growth factor for diabetic macular oedema: A network meta-analysis**
Cochrane Database Syst Rev. 2018; 10: CD007419
**Purpose**: To compare the effectiveness and safety of the different anti-VEGF drugs using network meta-analysis methods.
**Results**: Included 24 studies with 6007 patients with DMO and moderate vision loss. Aflibercept, bevacizumab, and ranibizumab were all more effective than laser therapy for improving vision by 3 or more lines after one year. Aflibercept may confer some advantage over ranibizumab and bevacizumab. There were no differences in adverse events.
**Conclusions**: Anti-VEGF drugs are effective at improving vision in people with DMO with three to four in every 10 people likely to experience an improvement of 3 or more lines VA at one year. More evidence on the long-term (greater than two years) comparative effects of these anti-VEGF agents is needed.



Clinically significant macular edema is defined as thickening of the retina at or within 500 µm of the centre of the macula



**Presence of DR in**
**Type 1 DM**
- 25% after 5 yr
- 60% after 10 yr
- >80% after 15 yr

**Type 2 DM**
- 20% at time of diagnosis
- 60% after 20 yr

### Extraocular Muscle Palsy
- usually CN III infarct
- pupil usually spared in diabetic CN III palsy, but ptosis is observed
- may involve CN IV and VI
- usually recover within few months

### Optic Neuropathy
- visual acuity loss due to infarction of optic disc/nerve

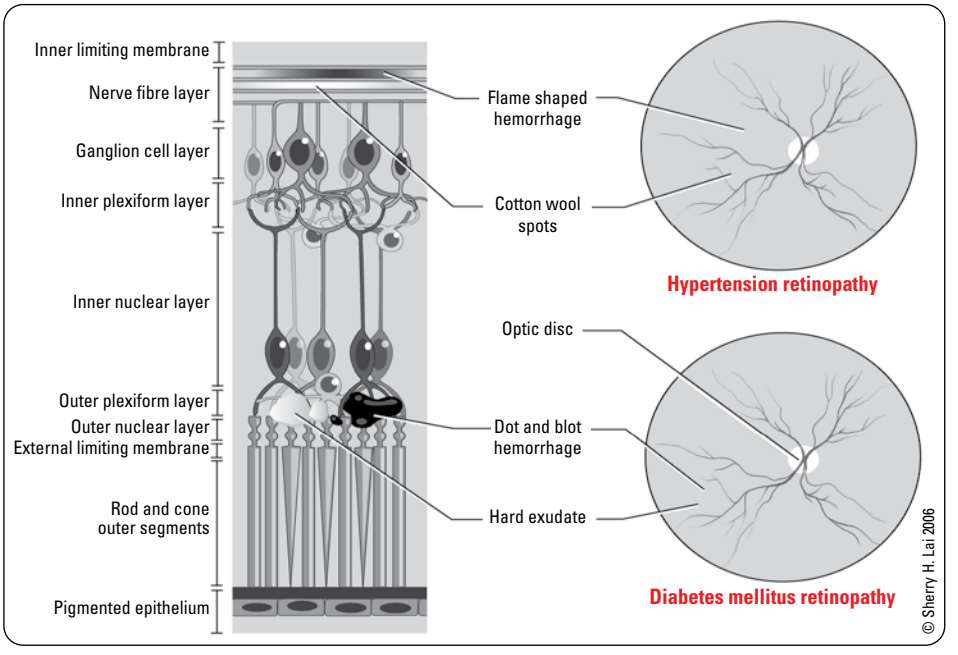



**Figure 24. DM vs. HTN retinopathy**

# Hypertension

- retinopathy is the most common ocular manifestation
- acute HTN retinopathy: retinal arteriolar spasm, superficial retinal hemorrhage, cotton wool spots, optic disc edema
- chronic HTN retinopathy: arteriovenous (AV) nicking, flame/blot retinal hemorrhages, cotton wool spots
- increases risk for many other ocular diseases (DR, BRVO, CRAO/BRAO)

**Table 10. Modified Scheie Classification**

| | |
|---|---|
| **Grade 0** | No changes |
| **Grade 1** | Mild arterial narrowing |
| **Grade 2** | Obvious arterial narrowing with focal irregularities |
| **Grade 3** | Grade 2 + retinal hemorrhages and/or exudate |
| **Grade 4** | Grade 3 + swollen optic nerve (malignant HTN) |

# Multiple Sclerosis

- see Neurology, N52

### Clinical Features
- blurred vision and decreased colour vision secondary to optic neuritis
- central scotoma due to damage to papillomacular bundle of retinal nerve fibres
- diplopia secondary to INO
- RAPD, ptosis, nystagmus, uveitis, optic atrophy, optic neuritis
- white matter demyelinating lesions of optic nerve on MRI

### Treatment
- IV steroids with taper to oral form for optic neuritis
  - DO NOT treat with oral steroids in isolation due to increased risk of developing MS

**Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: 2 Year Result from a Comparative Effectiveness Randomized Clinical Trial**
Ophthalmology 2016;123:1351-1359
All 3 anti-VEGF groups showed improvement of VA and deceased number of injections in year 2. Among eyes with worse baseline VA, aflibercept had superior 2 yr VA compared with bevacizumab, but superiority over ranibizumab in year 1 was no longer identified.

**Effects of Medical Therapies on Retinopathy Progression in Type 2 DM**
NEJM 2010;363:233-244
**Purpose**: To determine whether intensive glycemic control, combination therapy for dyslipidemia, and intensive blood pressure control may limit the progression of DR in persons with type 2 DM.
**Methods**: RCT with 10,251 participants with type 2 DM at high risk of cardiovascular disease. Intensive or standard treatment for glycemia (glycated hemoglobin level <6.0% or 7.0-7.9%), dyslipidemia (160 mg daily fenofibrate plus simvastatin or placebo plus simvastatin), or systolic blood-pressure control (target <120 or <140 mmHg).
**Results**: Rates of progression of DR at 4 yr were 7.3% with intensive glycemia treatment vs. 10.4% with standard therapy (OR 0.67; 95% CI 0.51-0.87); 6.5% with fenofibrate for intensive dyslipidemia therapy vs. 10.2% with placebo (OR 0.60; 95% CI 0.42-0.87) and 10.4% with intensive blood pressure therapy vs. 8.8% with standard therapy (OR 1.23; 95% CI 0.84-1.79).
**Conclusions**: Intensive glycemic control and intensive combination treatment of dyslipidemia, but not intensive blood pressure control, reduced the rate of DR.

**Corticosteroids for Treating Optic Neuritis**
Cochrane Database Syst Rev 2015;8:CD001430
**Summary**: no conclusive evidence of benefit in terms of recovery to normal visual acuity, visual field, or contrast sensitivity six mo after initiation of IV or oral corticosteroids.
**Results**: after review of 6 RCTs evaluating systemic corticosteroids for treatment of acute optic neuritis, all meta-analyses show similar outcomes for placebo vs. corticosteroid group for visual acuity, contrast sensitivity, and visual field.

# TIA/Amaurosis Fugax

- sudden, transient blindness from intermittent vascular compromise
- ipsilateral carotid most frequent embolic source
- typically monocular, lasting <5-10 min
- Hollenhorst plaques (glistening microemboli seen at branch points of retinal arterioles)

# Graves' Disease

- ophthalmopathy occurs despite control of thyroid gland status
- ocular manifestations occur secondary to sympathetic overdrive and/or specific inflammatory infiltrate of the orbital tissue

The most common cause of unilateral or bilateral proptosis in adults is Graves' disease

### Clinical
- initial inflammatory phase is followed by a quiescent cicatricial phase

### Treatment
- treat hyperthyroidism
- monitor for corneal exposure and maintain corneal hydration
- manage diplopia, proptosis, and compressive optic neuropathy with one or a combination of:
  - steroids (during acute phase)
  - orbital bony decompression
  - external beam radiation of the orbit
- consider strabismus and/or eyelid surgical procedures once acute phase subsides

**Progression of Signs and Symptoms of Graves' Ophthalmopathy**

**NO SPECS**
**N**o signs/symptoms
**O**nly signs (lid retraction, lid lag)
**S**oft tissue swelling (periorbital edema)
**P**roptosis (exophthalmos)
**E**xtraocular muscle weakness (causing diplopia)
**C**orneal exposure
**S**ight loss

# Connective Tissue Disorders

- RA, juvenile idiopathic arthritis, SLE, Sjögren's syndrome, ankylosing spondylitis, polyarteritis nodosa
- most common ocular manifestation: dry eyes (keratoconjunctivitis sicca)

# Giant Cell Arteritis/Temporal Arteritis

- see Rheumatology, RH21

### Clinical Features
- more common in women >60 yr
- abrupt monocular loss of vision, pain over the temporal artery, jaw claudication, scalp tenderness, constitutional symptoms, and PMHx of polymyalgia rheumatica
- ischemic optic atrophy
- 50% lose vision in contralateral eye if untreated

**ESR in Temporal Arteritis**
Males >age/2
Females >(age + 10)/2

### Diagnosis
- temporal artery biopsy + increased ESR and CRP (ESR can be normal, but likely 80-100 in first hour)
- if biopsy is negative, biopsy contralateral side

**Does this Patient have Temporal Arteritis?**
JAMA 2002;287:92-101
**Rule in**: jaw claudication and diplopia on history, temporal artery beading, prominence of the artery and tenderness over the artery on exam.
**Rule out**: no temporal artery abnormalities on exam, normal ESR.

### Treatment
- high dose corticosteroid to relieve pain and prevent further ischemic episodes
- if diagnosis of GCA is suspected clinically: start STAT treatment + perform temporal artery biopsy to confirm diagnosis within 2 wk of initial presentation

# Sarcoidosis

### Definition
- granulomatous uveitis with large "mutton fat" keratitic precipitates and posterior synechiae
- complications include glaucoma, cataracts, retinal hemorrhages, peripheral retina neovascularization, and dry eye
- neurosarcoidosis: optic neuropathy, oculomotor abnormalities, visual field loss

### Treatment
- topical/systemic steroids and mydriatics

# Pediatric Ophthalmology

## Strabismus

- ocular misalignment in one or both eyes, can be found in up to 3% of children
- **classification**
  - manifest (constant) vs. latent (hidden) alignment
  - comitant (deviation equal in all positions of gaze, also known as non-paralytic or concomitant) vs. incomitant (deviation worse in certain positions, also known as paralytic or restrictive)
  - described in direction of deviation relative to the fixating eye
- distinguish from pseudostrabismus (prominent epicanthal folds, hypertelorism)
- complications: amblyopia, cosmesis

Strabismus in children under 4 mo of age sometimes resolves, particularly if the deviation is intermittent, variable, or measures <40 prism diopters

All children with strabismus and/or possible reduced vision require prompt referral to an ophthalmologist

### HETEROTROPIA

- manifest deviation
- deviation not corrected by the fusion mechanism (i.e. deviation is apparent when the patient is using both eyes)

### HETEROPHORIA

- latent deviation
- deviation corrected in the binocular state by the fusion mechanism (i.e. deviation not seen when patient is focusing with both eyes)
- very common – majority are asymptomatic
- may be exacerbated or become manifest with asthenopia (eye strain, fatigue)

### Types

- exo- (lateral deviation), eso- (medial deviation)
- hyper- (upward deviation), hypo- (downward deviation)
- esotropia = "crossed-eyes"; exotropia = "wall-eyed"

### Tests

- Hirschberg test (corneal light reflex): positive if the light reflex on both corneas is asymmetrical
  - false positives occur if visual axis and anatomic pupillary axis of the eye are not aligned (angle κ)
  - positive in -tropias; negative in -phorias
- cover-uncover test allows to differentiate between -tropias and -phorias
  - any movement of the non-occluded eye in a single cover test indicates a -tropia, as that eye picks up fixation in the absence of visual input to the dominant eye
  - any movement of the occluded eye in a cover-uncover test indicates a -phoria
- alternate cover test
  - alternating the cover between both eyes reveals the total deviation, both latent and manifest
  - maintain cover over one eye for 2-3 s before rapidly shifting to other eye
  - deviation can be quantified using a prism over one eye (alternate prism cover test)

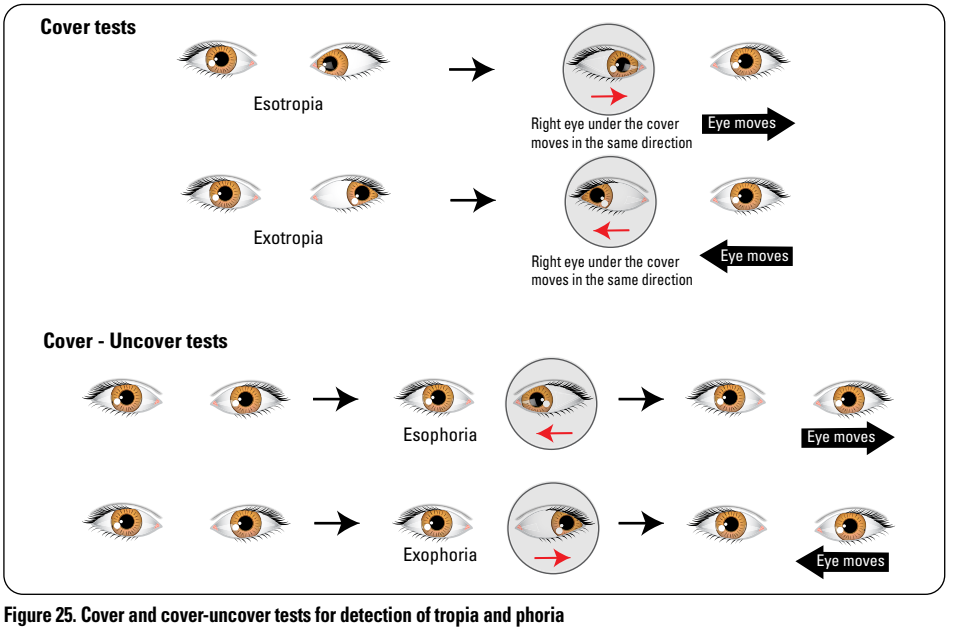



Figure 25. Cover and cover-uncover tests for detection of tropia and phoria

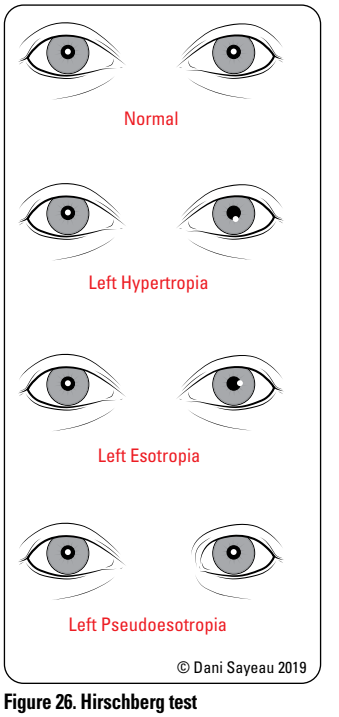



Figure 26. Hirschberg test

**Table 11. Paralytic vs. Non-Paralytic Strabismus**

| Clinical Characteristics | Paralytic Strabismus | Non-paralytic Strabismus |
|---|---|---|
| **Definition** | Incomitant strabismus | Concomitant strabismus |
| **Onset** | Often sudden but may be gradual or congenital | Usually gradual or shortly after birth; rarely sudden |
| **Age of Onset** | Any age; most often acquired | Usually during infancy |
| **Etiology** | Reduction or restriction in range of eye movements due to:<br>Neural (CN III, IV, VI): ischemia (e.g. DM), MS, aneurysm, brain tumour, trauma<br>Muscular: myasthenia gravis (neuromuscular junction pathology), Graves' disease<br>Structural: restriction or entrapment of extraocular muscles due to orbital inflammation, tumour, fracture of the orbital wall | Develops early in childhood<br>No restriction in range of eye movements<br>Monocular, alternating, or intermittent |
| **Diplopia** | Common | Uncommon; image from the misaligned eye is suppressed |
| **Visual Acuity in Other Eye** | Usually unaffected in the other eye, unless CN II is involved | Deviated eye may become amblyopic if not treated when the child is young<br>Amblyopia treatment rarely successful after age 8-10 yr<br>Amblyopia usually does not develop if child has alternating strabismus or intermittency, which allows neural pathways for both eyes to develop |
| **Possibility of Amblyopia** | Uncommon | Common |
| **Neurologic Findings or Systemic Disease** | May be present | Usually absent |

### Accommodative Esotropia
- normal response to approaching object is the triad of the near reflex: convergence, accommodation, and miosis
- hyperopes must constantly accommodate – excessive accommodation can lead to esotropia in young children via over-activation of the near reflex
- average age of onset is 2.5 yr
- usually reversible with correction of refractive error

### Non-Accommodative Esotropia
- accounts for 50% of childhood strabismus
- most are idiopathic
- may be due to monocular visual impairment (e.g. cataract, corneal scarring, anisometropia, retinoblastoma) or divergence insufficiency (ocular misalignment that is greater at distance fixation than at near fixation)

### Exotropia
- accounts for 11-18% of childhood strabismus
- congenital: onset before 6 mo, may be associated with other conditions (e.g. neurologic, craniofacial disorders)
- acquired
  - intermittent exotropia: typically apparent when patient is tired of looking in the distance
  - sensory exotropia: eye with poorer vision drifts outward (age ≥2)
  - consecutive exotropia: develops after strabismus surgery

## Amblyopia

### Definition
- most common cause of vision loss in children; a neurodevelopmental visual disorder with unilateral or bilateral (less common) reduction of BCVA that cannot be attributed only to the effect of an ocular structural abnormality
- cannot be remedied immediately by prescription eyewear alone
- errors, anisometropia (asymmetric refractive errors), and concomitant structural ocular problems

### Etiology
- progressive suppression of visual input from eye receiving suboptimal image (blurry, deviated)
- in approximately half of the cases, amblyopia is secondary to strabismus (mainly esotropia)
- other causes may include uncorrected refractive errors, anisometropia (asymmetric refractive errors, usually in the more hyperopic eye), and deprivation due to structural ocular problems (ptosis, cataract, corneal opacity/scarring, retinoblastoma)

### Diagnosis
- "Holler Test": young child upset if good eye is covered
- quantitative visual acuity by age 3-4 yr using picture charts and/or matching game (Sheridan-Gardiner), testing each eye separately

### Management
- strabismus
  - correct with glasses for accommodative esotropia
  - occlusion therapy (see below)
  - surgery: recession (weakening) by moving muscle insertion further back on the globe or resection (strengthening) by shortening the muscle
  - botulinum toxin for single muscle weakening
  - after ocular alignment is restored (glasses, surgery, botulinum toxin), patching is frequently necessary to maintain vision until ~8 yr of age
  - no proven value for vision training in the treatment of strabismus or amblyopia
- anisometropia
  - the more emmetropic (normally-refracting) eye receives a clear image, while the less emmetropic eye receives a blurred image; input from the blurred eye is cortically suppressed and visual pathway fails to develop normally
  - treat with glasses to correct refractive error
  - patching is required if visual acuity difference persists after using glasses for 4-8 wk
- deprivation: treat underlying cause
- amblyopia treatment less successful after age 8-10 yr, but a trial should be given no matter what age
  - prognosis: 90% will have good vision restored and maintained if treated before age 4

### Occlusion Therapy
- patching the good eye to force the brain to use the non-dominant eye and redevelop its vision with follow-up to prevent occlusion ambylopia
- cycloplegic drops (e.g. atropine) to impair accommodation and blur vision of the good eye

### Risks
- permanent loss of vision in the affected eye
- possibility of injury to "remaining" good eye (e.g. occlusion amblyopia)
- safety glasses or polycarbonate lenses recommended if visual acuity in worse eye is <20/50
- loss of stereopsis

## Leukocoria

### Definition
- white reflex (red reflex is absent)
- the presence of leukocoria warrants urgent referral to an ophthalmologist

### Differential Diagnosis
- retinoblastoma
- cataract
- Coats disease (exudative retinal telangiectasis)
- persistent hyperplastic primary vitreous or persistent fetal vasculature
- retinal coloboma (chorioretinal)
- RD
- congenital infections, e.g. toxoplasmosis and toxocariasis
- ROP

## Retinoblastoma

### Definition
- intraocular malignancy that rapidly develops from immature cells of the retina

### Epidemiology
- most common primary intraocular malignancy in children
- incidence: 1/15000
- unilateral (2/3) or bilateral (1/3)
- malignant – direct or hematogenous spread

### Etiology
- sporadic or genetic transmission; screening of siblings/offspring essential
- inherited forms likely to be bilateral
- often caused by mutations in RB1 on ch13q14, the first tumour suppressor gene discovered, and less commonly by amplifications of MYCN, an oncogene

### Diagnosis
- often presents with leukocoria and/or strabismus
- others signs: red eye, eye enlargement if advanced disease
- fundus examination (nodular, white/cream-coloured masses with intralesional blood vessels)
- CT, U/S (A & B-scan), or MRI may demonstrate RD and/or calcified mass (present in most cases)

### Treatment
- local (laser, cryotherapy), systemic (radiotherapy, chemotherapy), and/or enucleation + genetic counselling

**Retinal Zones**
- Zone I: circle with radius twice the distance from the disc to the macula (most difficult to treat)
- Zone II: annulus from zone I to nasal extent of retina (nasal ora serrata)
- Zone III: remaining retina

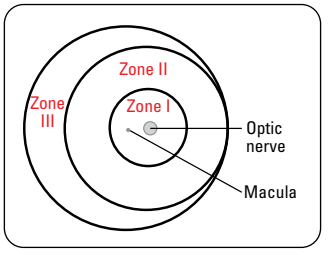



**Figure 27. Zones of the retina in ROP**

# Retinopathy of Prematurity

### Definition
- vasoproliferative retinopathy that is a major cause of blindness in the developed world

### Risk Factors
- non-black race (black infants have lower risk of developing ROP)
- earlier gestational age, birth weight <1500 g, low caloric intake, postnatal hyperglycemia,
- high oxygen exposure after birth (iatrogenic), i.e. assisted ventilation >1 wk

### Classification (ROP Staging)
- stage 1: flat white demarcation line at the junction between the vascular and avascular retina
- stage 2: elevated ridge
- stage 3: extra-retinal fibrovascular tissue extending into vitreous
- stage 4: partial RD (4A: macula "on", 4B: macula "off")
- stage 5: total RD
- plus (+) disease: dilatation and tortuosity of retinal vessels
- threshold disease: stage 3+ in zones 1 or 2 with circumferential extent of ROP involvement in 5 continuous or 8 cumulative clock hours (1-12)

### Treatment
- laser ablation is currently the treatment standard for stages 1-3; intravitreal bevacizumab showed significant benefits in zone I compared to laser ablation therapy in infants with stage 3+ ROP
- stage 4-5 is treated with vitrectomy/scleral buckle (goal is to release vitreous tractional forces on the retina)

### Prognosis
- higher incidence of myopia among ROP infants, even if treated successfully
- stage 4B and 5 have poor prognosis for visual outcome despite treatment

**Anti-VEGF Drugs for Treatment of Retinopathy of Prematurity (ROP)**
Cochrane Database Syst Rev 2018;1:CD009734
**Summary/Conclusions**: Review of 6 RCTs/Quasi-RCTs comparing anti-VEGF agents vs. conventional therapy for ROP (n=383).
- Insufficient data precludes strong conclusions for routine use of intravitreal anti-VEGF agents for treatment of ROP
- Intravitreal bevacizumab/ranibizumab as monotherapy reduces risk of refractory errors during childhood.
- Intravitreal pegaptanib + laser therapy reduces the risk of retinal detachment for type 1 ROP
- Effect on other critical outcomes and long-term systemic adverse effects are unknown

# Nasolacrimal System Defects

### Definition
- congenital obstruction of the nasolacrimal duct (failure of canalization) at valve of Hasner, ~1-2 mo of age

### Signs and Symptoms
- epiphora (overflow of tears), periocular crusting, mucopurulent discharge, recurrent conjunctivitis
- can have reflux of mucopurulent material from lacrimal punctum when pressure is applied over lacrimal sac

### Treatment
- circular massage over lacrimal sac at medial canthus
- vast majority spontaneously resolve in 9-12 mo, otherwise consider referral for duct probing

# Ophthalmia Neonatorum

### Definition
- purulent conjunctivitis with profuse exudate in the first few days of life; can cause blindness

### Etiology
- chemical/toxic: silver nitrate, erythromycin (secondary to prophylaxis, self-limiting)
- infectious: bacterial (e.g. *N. gonorrhoeae* – most common, *C. trachomatis*), herpes simplex virus

### Treatment
- systemic antibiotics and saline irrigation with possible hospitalization if infectious etiology

Gonococcal infection is the most serious threat to sight as it can rapidly penetrate corneal epithelium, causing corneal ulceration

# Congenital Glaucoma

### Definition
- elevated IOP within the first year of life

### Etiology
- not entirely known – may be due to inadequate development of anterior chamber
- sporadic and hereditary (autosomal recessive); males more often affected
- secondary congenital glaucoma can be associated with ocular and systemic disorders
  - ocular: aniridia, microcornea, megalocornea, cornea plana, iridoschisis, microphthalmos, persistent hyperplastic primary vitreous, posterior polymorphous dystrophy
  - systemic: Prader-Willi, trisomies, fetal alcohol syndrome, mucopolysaccharidoses, and many others

Epiphora in children – rule out congenital glaucoma

### Clinical Features
- photophobia, epiphora, and blepharospasm
- cloudy cornea due to edema; Haab's striae due to breaks in Descemet's membrane
- increased IOP, rapidly-progressive myopia
- buphthalmos (large cornea, "ox eye") and enlarged C:D

### Treatment
- immediate filtration surgery after birth

# Ocular Trauma

## Blunt Trauma

- caused by blunt object such as fist
- HPI: injury, ocular history, drug allergy, tetanus status
- PEx: VA first, pupil size and reaction, EOM (diplopia), external and slit-lamp exam, ophthalmoscopy
  - if VA normal or slightly reduced: globe less likely to be perforated
  - if VA reduced: possible globe perforation, corneal abrasion, lens dislocation, retinal tear
- bone fractures
  - blow out fracture: restricted EOM, diplopia, enophthalmos (sunken eye)
  - ethmoid fracture: subcutaneous emphysema of lid
- lids: swelling, laceration, emphysema
- conjunctiva: subconjunctival hemorrhage
- cornea: abrasion (detect with fluorescein staining and cobalt blue filter using slit-lamp or ophthalmoscope)
- anterior chamber: assess depth, hyphema, hypopyon
- iris: prolapse, iritis
- lens: cataract, dislocation
- vitreous: hemorrhage
- retina: tear, detachment

Always test VA first – medicolegal protection

**Refer if You Observe Any of These Signs**
- Decreased VA
- Shallow anterior chamber
- Hyphema
- Abnormal pupil
- Ocular misalignment
- Retinal damage

## Penetrating Trauma

- includes: ruptured globe ± lid laceration, prolapsed iris, intraocular foreign body
- rule out intraocular foreign body with CT orbit, especially if history of "metal striking metal"
- **OCULAR EMERGENCY**: initial management - REFER IMMEDIATELY
  - ABCs
  - avoid pressing on eye globe
  - avoid checking IOP
  - check vision, diplopia
  - apply rigid eye shield to minimize further trauma
  - keep head elevated 30-45° to keep IOP down
  - keep NPO
  - tetanus status
  - give IV antibiotics
    - selecting appropriate agents depends on the mechanism of injury; Gram-positive bacteria are more commonly involved than Gram-negative; retained intraocular foreign objects increase the risk of infections with *Bacillus* species, whereas exposure to vegetable matter increase the risk of a fungal etiology

**Management of Suspected Globe Rupture**
**CAN'T** forget
**CT** orbits
**A**ncef (cefazolin) ± Aminoglycoside IV
**N**PO
**T**etanus status

**Post-Traumatic Infectious Endophthalmitis**
Surv Ophthalmol 2011;56:214-251
- Delayed primary repair (>24 h after open globe injury) increases risk for post-traumatic endophthalmitis in the absence of an intraocular foreign body (IOFB).
- If IOFB present, early vitrectomy and IOFB removal must be performed within 24 h of injury.
- Extreme pain with hypopyon and vitritis indicate endophthalmitis until proven otherwise, and samples must be obtained.
- Treat with empirical intravitreal and intravenous antibiotic guided by nature of trauma, and adjust based on culture.

## Hyphema

### Definition
- blood in anterior chamber, often due to damage to root of the iris
- may occur with blunt trauma

### Treatment
- refer to ophthalmology
- shield and bedrest for 5 d or as determined by ophthalmologist
- sleep with head upright
- may need surgical drainage if hyphema persists or if re-bleed

### Complications
- risk of re-bleed highest on day 2-5, and may result in secondary glaucoma, corneal staining, and iris necrosis
- never prescribe Aspirin® (increases risk of re-bleed)

**Shaken Baby Syndrome**
Syndrome of findings characterized by absence of external signs of abuse with respiratory arrest, seizures, or coma. Ocular exam findings are important diagnostically for Shaken Baby Syndrome. These findings include extensive retinal and vitreous hemorrhages that occur during the shaking process and are extremely rare in accidental trauma. A detailed fundoscopic exam or an ophthalmology referral should be conducted for all infants in whom abuse is suspected

**Classic Signs of Blow-Out**
- Enophthalmos
- Decreased upgaze (inferior rectus trapped)
- Cheek anesthetized (infraorbital nerve trapped)

# Blow-Out Fracture

• see Plastic Surgery, PL33

### Definition
- blunt trauma causing fracture of orbital floor and herniation of orbital contents into maxillary sinus
- orbital rim remains intact
- inferior rectus and/or inferior oblique muscles may be incarcerated at fracture site
- infraorbital nerve courses along the floor of the orbit and may be damaged

### Clinical Features
- pain and nausea at time of injury
- diplopia, restriction of EOM
- infraorbital and upper lip paresthesia or anesthesia (CN V2)
- enophthalmos (sunken eye), periorbital ecchymoses

### Investigations
- plain films: Waters' view (occipitomental view)
- CT: anteroposterior and coronal view of orbits

### Treatment
- refrain from coughing, blowing nose
- systemic antibiotics may be indicated
- surgery if fracture >50% orbital floor, diplopia not improving, or enophthalmos >2 mm
- may delay surgery if the diplopia improves

# Chemical Burns

- alkali burns have a worse prognosis than acid burns because acids coagulate tissue and inhibit further corneal penetration
- poor prognosis if cornea opaque, likely irreversible stromal damage
- even with a clear cornea initially, alkali burns can progress for weeks – thus, very guarded prognosis

### Treatment
- immediately irrigate site of accident with water or balanced saline solution (BSS)
  - irrigate with eyelids retracted in emergency department with IV drip to physiologic pH (test with litmus paper)
  - swab upper and lower fornice to remove possible particulate matter
- do not attempt to neutralize an acid with a base, or vice versa
- topical antibiotics and patching
- cycloplegic drops to decrease iris spasm (pain) and prevent secondary glaucoma (due to posterior synechiae formation)
- topical antibiotics and patching
- topical steroids (prescribed by ophthalmologist) to decrease inflammation, use for <2 wk in the case of a persistent epithelial defect

# Ocular Drug Toxicity

**Table 12. Drugs with Ocular Toxicity**

| | |
|---|---|
| **Amiodarone** | Corneal microdeposits and superficial keratopathy (vortex keratopathy)<br>Rare: ischemic optic neuropathy |
| **Atropine, benztropine** | Pupillary dilation (risk of angle-closure glaucoma) |
| **Bisphosphonates (Fosamax®, Actonel®)** | Inflammatory eye disease (iritis, scleritis, episcleritis) |
| **Chloroquine, hydroxychloroquine** | Bull's eye maculopathy<br>Vortex keratopathy |
| **Chlorpromazine** | Anterior subcapsular cataract |
| **Contraceptive pills** | Decreased tolerance to contact lenses<br>Migraine<br>Optic neuritis<br>Central vein occlusion, benign increase in intracranial pressure |
| **Digitalis** | Yellow vision<br>Blurred vision |
| **Ethambutol** | Optic neuropathy |
| **Haloperidol (Haldol®)** | Oculogyric crises<br>Blurred vision |
| **Indomethacin** | Superficial keratopathy |

**Table 12. Drugs with Ocular Toxicity** (continued)

| | |
|---|---|
| **Interferon** | Retinal hemorrhages and cotton wool spots |
| **Isoniazid** | Optic neuropathy |
| **Nalidixic acid** | Papilledema |
| **Steroids** | Posterior subcapsular cataracts<br>Glaucoma<br>Papilledema (systemic steroids)<br>Increased severity of HSV infections (geographic ulcers)<br>Predisposition to fungal infections |
| **Sulphonamides, NSAIDs** | Stevens-Johnson syndrome |
| **Tamsulosin (Flomax®)** | Intraoperative floppy iris syndrome (can complicate cataract surgery) |
| **Tetracycline** | Papilledema (associated with pseudotumour cerebri) |
| **Thioridazine** | Pigmentary degeneration of retina |
| **Vigabatrin** | Retinal deposition with macular sparing, peripheral visual field loss |
| **Vitamin A toxicity** | Papilledema |
| **Vitamin D toxicity** | Band keratopathy |

# Common Medications

## TOPICAL OCULAR DIAGNOSTIC DRUGS

### Fluorescein Dye
- water-soluble orange-yellow dye
- green under cobalt blue light (ophthalmoscope, slit-lamp ± applanation tonometry)
- absorbed in areas of epithelial loss (ulcer, abrasion, laceration)
- stains mucus, contact lenses, foreign bodies

### Rose Bengal Stain
- stains devitalized epithelial cells and mucus to indicate tear film abnormalities (e.g. mucin deficiency)

### Anesthetics
- e.g. proparacaine HCl 0.5%, tetracaine 0.5%
- indications: removal of foreign body and sutures, tonometry, examination of painful cornea
- toxic to corneal epithelium (inhibit mitosis and migration) and can lead to corneal ulceration and scarring with prolonged use, therefore NEVER prescribe

### Mydriatics
- dilate pupils
- two classes
  - cholinergic blocking (e.g. tropicamide – Mydriacyl®)
    - dilation plus cycloplegia (loss of accommodation) by paralysis of iris sphincter and the ciliary body
    - indications: refraction, ophthalmoscopy, therapy for iritis
  - adrenergic stimulating (e.g. phenylephrine HCl 2.5%)
    - stimulate pupillary dilator muscles, no effect on accommodation
    - usually used with tropicamide for additive effects
    - side effects: HTN, tachycardia, arrhythmias

**Table 13. Mydriatic Cycloplegic Drugs and Duration of Action**

| Drugs | Duration of Action |
|---|---|
| Tropicamide (Mydriacyl®) 0.5%, 1% | 4-5 h |
| Cyclopentolate HCl 0.5%, 1% | 3-6 h |
| Homatropine HBr 1%, 2% | 3-7 d |
| Atropine sulfate 0.5%, 1% | 1-2 wk |
| Scopolamine HBr 0.25%, 5% | 1-2 wk |



| | |
|---|---|
| **Green** | Cholinergics |
| **Red** | Anti-cholinergics |
| **White** | Anesthetics, antibiotics, artificial tears, steroids |
| **Yellow** | β-blockers |
| **Blue** | β-blocker combinations |
| **Purple** | α-agonists |
| **Teal** | Prostaglandins |
| **Orange** | Carbonic anhydrase inhibitors |
| **Tan** | Fluoroquinolones |
| **Grey** | NSAIDs |
| **Pink** | Anti-inflammatories, steroids |

## GLAUCOMA MEDICATIONS

**Table 14. Glaucoma Medications**

| Drug Category | Dose | Effect | Comment/Side Effects |
|---|---|---|---|
| **α-Agonist**<br>**Non-selective**<br>• epinephrine HCl 1% (Epifrin®)<br>• dipivalyl epinephrine 0.1% (Propine®)<br>**α2-selective**<br>• brimonidine 0.2% (Alphagan®)<br>• apraclonidine 0.5% (Iopidine®) | 1 gtt OS/OD bid/tid | 1. Non-selective: reduced aqueous production + increased TM outflow<br>2. Selective: reduced aqueous production + increased uveoscleral outflow | 1. Non-selective: mydriasis, macular edema, tachycardia<br>2. Selective: contact allergy, hypotension in children |
| **β-Blocker**<br>**Non-selective**<br>• timolol (Timoptic®)<br>• levobunolol (Betagan®)<br>**β 1-selective**<br>• betaxolol (Betoptic®) | 1 gtt OS/OD qd/bid | Reduced aqueous production | **Bronchospasm (caution in asthma/COPD)**<br>Increased CHF<br>Bradycardia, hypotension, depression, heart block, impotence |
| **Carbonic Anhydrase Inhibitor**<br>• dorzolamide (Trusopt®)<br>• brinzolamide (Azopt®)<br>• oral: acetazolamide (Diamox®), methazolamide (Neptazane®) | 1 gtt OS/OD tid<br>Diamox®: 500 mg PO bid | Reduced aqueous production | **Must ask about sulfa allergy**<br>Generally local side effects with topical preparations<br>Oral: diuresis, fatigue, paresthesia, GI upset |
| **Parasympathomimetic**<br>(cholinergic stimulating)<br>• pilocarpine (Pilopine®)<br>• carbachol (Isopto Carbachol®) | 1-2 gtts OS/OD tid/qid | Increased TM outflow | Miosis<br>Reduced night vision<br>Increased GI motility, brow ache, headache<br>Reduced heart rate |
| **Prostaglandin Analogues**<br>• latanoprost (Xalatan®)<br>• travaprost (Travatan®)<br>• bimatoprost (Lumigan®) | 1 gtt OS/OD qhs | Increased uveoscleral outflow (uveoscleral responsible for 20% of drainage) | Iris colour change<br>Periorbital skin pigmentation<br>Lash growth<br>Conjunctival hyperemia |

Cosopt® = timolol + dorzolamide; Xalacom® = timolol + lantanoprost; Combigan® = timolol + brimonidine; DuoTrav® = tinolol + travaprost; gtt = drop, gtts = drops

## WET AGE-RELATED MACULAR DEGENERATION MEDICATIONS

### VEGF Inhibitors (Anti-VEGF)

- anti-VEGF agents prevent ocular angiogenesis and further development of choroidal neovascularization
- administered via intravitreal injections
- alflibercept (Eylea®) is a VEGF "trap" agent that binds VEGF-A, B, and placental growth factor
- ranibizumab (Lucentis®) is a monoclonal Fab fragment and non-selective anti-VEGF agent
- bevacizumab (Avastin®) is recombinant humanized monoclonal antibody and non-selective anti-VEGF agent
  - FDA approved only for metastatic breast cancer, colorectal cancer, and non-small cell lung cancer; therefore, its widespread ophthalmologic use is off-label

**Intravitreal Bevacizumab Versus Ranibizumab for Treatment of Neovascular Age-Related Macular Degeneration: Findings from a Cochrane Systematic Review**
Ophthalmology 2016; 123(1):70-77
**Summary:** In 6 RCTs with 2809 participants, there were no important differences in effectiveness or safety between bevacizumab and ranibizumab, despite a significant cost difference.

## TOPICAL OCULAR THERAPEUTIC DRUGS

### NSAIDs

- used for less serious chronic inflammatory conditions
- e.g. ketorolac (Acular®), diclofenac (Voltaren®), nepafenac (Nevanac®) drops

### Anti-Histamines

- used to relieve red and itchy eyes, often in combination with decongestants
- sodium cromoglycate – stabilizes membranes
- Olopatadine (Patanol®, Patady®)

### Decongestants

- weak adrenergic stimulating drugs (vasoconstrictor)
- e.g. naphazoline, phenylephrine (Isopto Frin®)
- rebound vasodilation with overuse; rarely can precipitate angle-closure glaucoma

### Antibiotics

- indications: bacterial and hyperpurulent conjunctivitis, corneal abrasions and ulcers, endophthalmitis, keratitis, blepharitis, globe rupture, cellulitis, lacrimal sac, and gland infections
- commonly as topical drops or ointments, may give systemically
- e.g. sulfonamide (sodium sulfacetamide, sulfisoxazole), gentamicin (Garamycin®), erythromycin, tetracycline, bacitracin, polymyxin B, fluoroquinolones (ciprofloxacin [Ciloxan®], ofloxacin [Ocuflox®], moxifloxacin [Vigamox®], gatifloxacin [Zymar®])

**Antiplatelet and Anticoagulant Drugs Do Not Affect Visual Outcome in Neovascular Age-Related Macular Degeneration in the BRAMD Trial**
Am J Ophthalmol 2018;187:130-137
**Summary:** In 330 NVAMD patients receiving either bevacizumab or ranibizumab treatment, use of anti-coagulant and anti-platelet agents was not associated with visual decline or occurrence of ocular hemorrhages.

### Corticosteroids

- e.g. fluorometholone (FML®), betamethasone, dexamethasone (Maxidex®), prednisolone (Predsol® 0.5%, Pred Forte® 1%), rimexolone (Vexol®), loteprednol etabonate 0.5% (Lotamax®), difluprednate (Durezol®)
- primary care physicians should avoid prescribing topical corticosteroids due to risk of glaucoma, cataracts, and reactivation of HSV keratitis
- complications
  - potentiates HSV keratitis and fungal keratitis as well as masking symptoms
  - increased IOP, more rapidly in steroid responders (within weeks)
  - posterior subcapsular cataract (within months)

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# OR Orthopedic Surgery

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# Acronyms

| | |
|---|---|
| ABI | ankle brachial index |
| AC | acromioclavicular |
| ACL | anterior cruciate ligament |
| AIN | anterior interosseous nerve |
| AP | anterior posterior |
| ARDS | acute respiratory distress syndrome |
| AVN | avascular necrosis |
| CA | coracoacromial |
| CC | coracoclavicular |
| CRPS | complex regional pain syndrome |
| C&S | culture and sensitivity |
| DDH | developmental dysplasia of the hip |
| DM | diabetes mellitus |
| DRUJ | distal radioulnar joint |
| DVT | deep vein thrombosis |
| EtOH | ethanol/alcohol |
| FAI | femoroacetabular impingement |
| FOOSH | fall on outstretched hand |
| GA | general anesthetic |
| HO | heterotopic ossification |
| I&D | incision and drainage |
| IM | intramedullary |
| LCL | lateral collateral ligament |
| MCL | medial collateral ligament |
| MT | metatarsal |
| MTP | metatarsophalangeal |
| MVC | motor vehicle collision |
| NVS | neurovascular status |
| NWB | non-weight bearing |
| OA | osteoarthritis |
| ORIF | open reduction internal fixation |
| PCL | posterior cruciate ligament |
| PE | pulmonary embolism |
| PIN | posterior interosseous nerve |
| RA | rheumatoid arthritis |
| ROM | range of motion |
| RSD | reflex sympathetic dystrophy |
| SCFE | slipped capital femoral epiphysis |
| SLAP | superior labrum, anterior posterior |
| SN | sensitivity |
| THA | total hip arthroplasty |
| TKA | total knee arthroplasty |
| TSA | total shoulder arthroplasty |
| WB | weight-bearing |
| # | fracture |

# Basic Anatomy Review

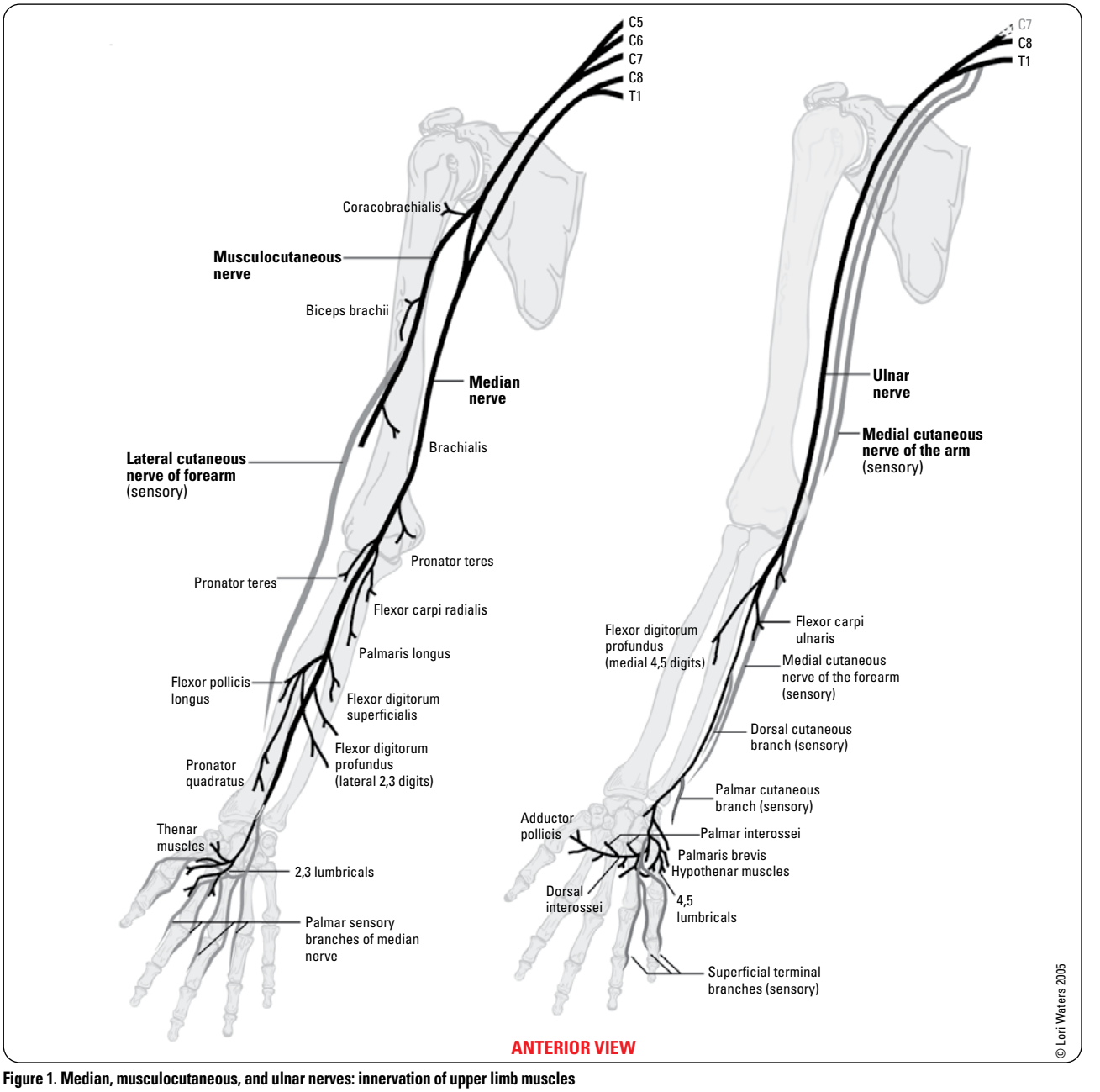



**Figure 1. Median, musculocutaneous, and ulnar nerves: innervation of upper limb muscles**

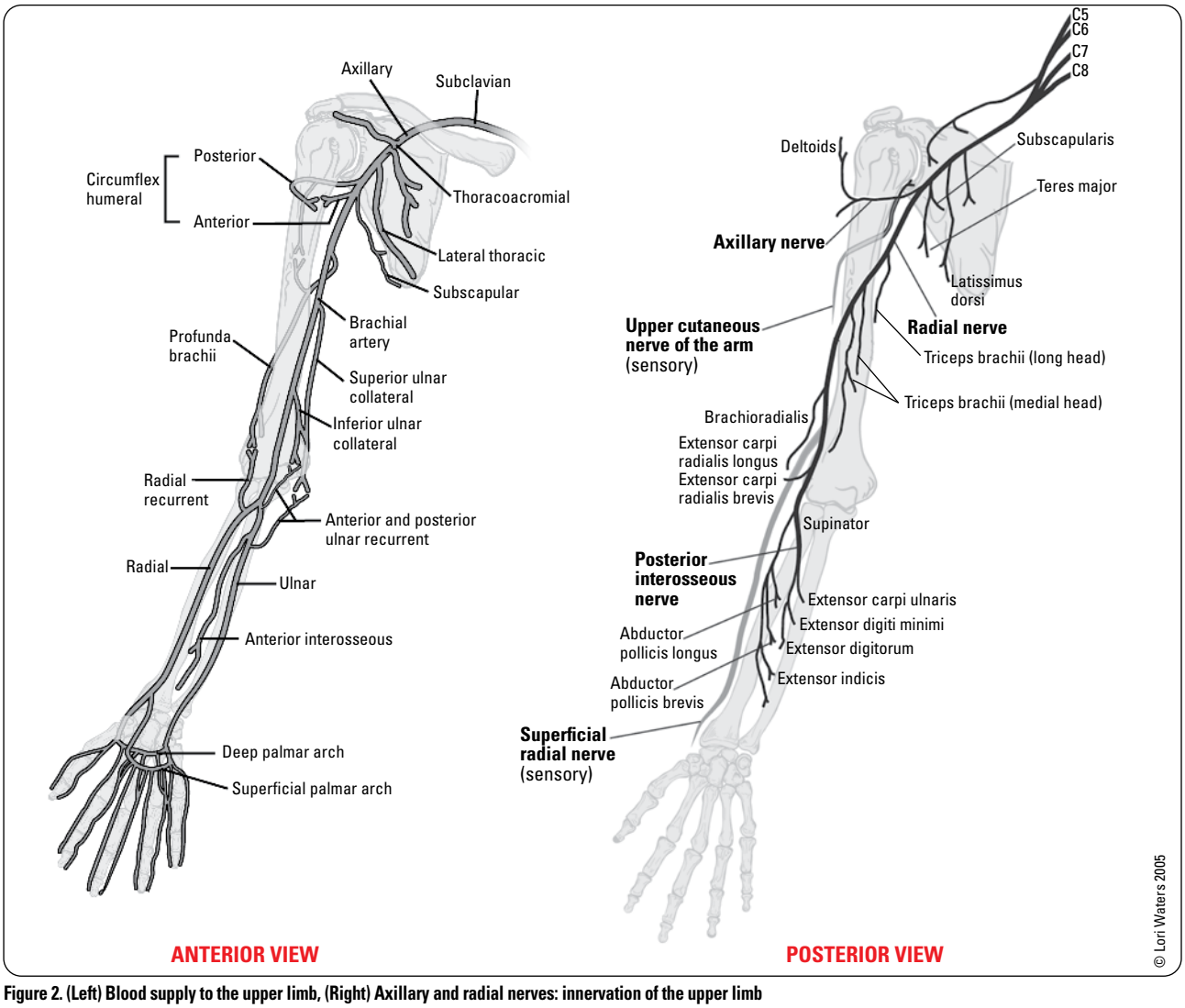



**Figure 2. (Left) Blood supply to the upper limb, (Right) Axillary and radial nerves: innervation of the upper limb**

**Table 1. Sensory and Motor Innervation of the Nerves in the Upper and Lower Extremities**

| Nerve | Motor | Sensory | Nerve Roots |
|---|---|---|---|
| **Axillary** | Deltoid/Teres Minor/Triceps (long head) | Lateral upper arm (Sergeant's Patch) | C5, C6 |
| **Musculocutaneous** | Biceps/Brachialis | Lateral forearm | C5, C6 |
| **Radial** | Triceps (medial and lateral heads)<br>Wrist/Thumb/Finger Extensors<br>Wrist abductors | Lateral dorsum of the hand<br>Medial upper forearm | C5, C6, C7, C8 |
| **Median** | Wrist flexors<br>Flexion of 1st-3rd digits | Palmar thumb to radial half of 4th digit, and the dorsal tips of digits 1 to radial half of digit 4 | C6, C7 |
| **Ulnar** | Wrist flexors and adductors<br>Flexion of 4th-5th digits | Medial palm and dorsum of hand<br>5th digit and medial half of 4th digit | C8, T1 |
| **Tibial** | Ankle plantar flexion<br>Knee flexion<br>Great toe flexion | Sole of foot | L5, S1 |
| **Superficial Peroneal** | Ankle eversion | Dorsum of foot | L5, S1 |
| **Deep Peroneal** | Ankle dorsiflexion and inversion<br>Great toe extension | 1st web space | L5, S1 |
| **Sural** | | Lateral foot | S1, S2 |
| **Saphenous** | | Anteromedial ankle | L3, L4 |

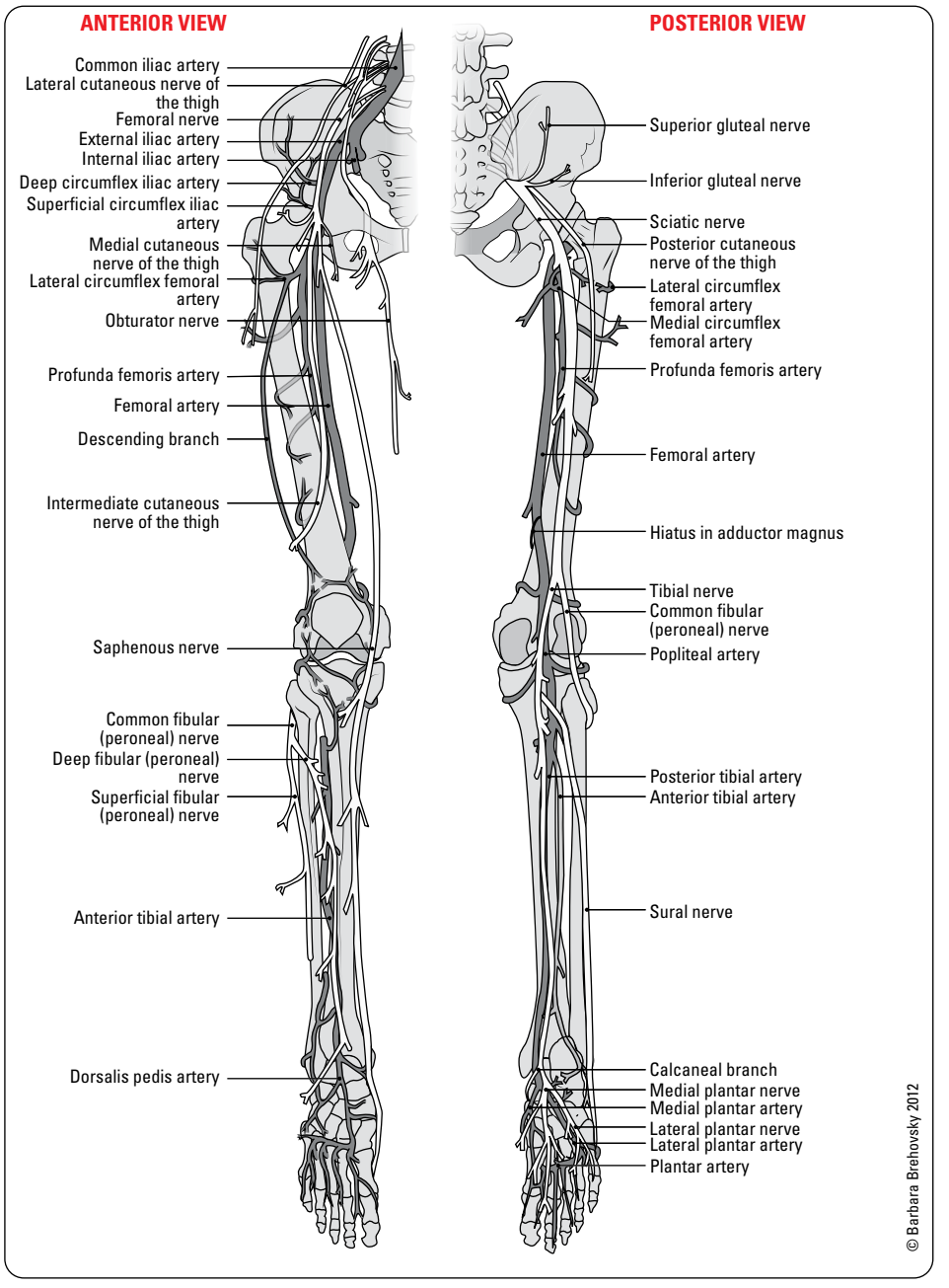



**Figure 3. Nerves and arteries of lower limbs**

**Table 2. Muscle and Compartment Review of the Limbs**

| | Arm | Forearm | Thigh | Leg |
|---|---|---|---|---|
| **Anterior Compartment** | Biceps Brachii<br>Brachialis<br>Coracobrachialis | Pronator Teres<br>Flexor Carpi Radialis<br>Palmaris Longus<br>Flexor Carpi Ulnaris<br>Flexor Digitorum Superficialis<br>Flexor Digitorum Profundus<br>Flexor Hallucis Longus<br>Pronator Quadratus | Sartorius<br>Quadriceps<br>Rectus Femoris<br>Vastus Lateralis<br>Vastus Intermedius<br>Vastus Medialis | Tibialis Anterior<br>Extensor Hallucis Longus<br>Extensor Digitorum Longus |
| **Posterior Compartment** | Triceps<br>Aconeus | Brachioradialis<br>Extensor Carpi Radialis Longus<br>Extensor Carpi Radialis Brevis<br>Extensor Carpi Ulnaris<br>Extensor Digitorum<br>Extensor Digiti Minimi<br>Abductor Pollicis Longus<br>Extensor Pollicis Longus<br>Extensor Pollicis Brevis<br>Extensor Indicis<br>Supinator | **Hamstrings**<br>Semitendinosus<br>Semimembranosus<br>Biceps Femoris | **Superficial**<br>Gastrocnemius<br>Soleus<br>Plantaris<br><br>**Deep**<br>Popliteus<br>Flexor Hallucis Longus<br>Flexor Digitorum Longus<br>Tibialis Posterior |
| **Medial Compartment** | | | Adductor Longus<br>Adductor Brevis<br>Adductor Magnus<br>Gracilis<br>Pectineus | |
| **Lateral Compartment** | | | | Fibularis Longus<br>Fibularis Brevis |

# Fractures – General Principles

## Fracture Description

### 1. Name of Injured Bone

### 2. Integrity of Skin/Soft Tissue
- closed: skin/soft tissue over and near fracture is intact
- open: skin/soft tissue over and near fracture is lacerated or abraded, such that fracture site communicates with outside environment, or contaminated (i.e. bowel)
- signs: continuous bleeding from puncture site, or fat droplets in blood are suggestive of an open fracture

### 3. Location
- epiphyseal: end of bone, forming part of the adjacent joint
- metaphyseal: the flared portion of the bone at the ends of the shaft
- diaphyseal: the shaft of a long bone (proximal, middle, distal)
- physis: growth plate

### 4. Orientation/Fracture Pattern (Figure 4)
- transverse: fracture line perpendicular (<30° of angulation) to long axis of bone; result of direct high energy force
- oblique: angular fracture line (30°- 60° of angulation); result of angulation and compressive force, high energy
- butterfly: triangular or wedge-shaped fragment resembling a butterfly; commonly between the two main fracture fragments in comminuted long bone fractures
- segmental: a separate segment of bone bordered by fracture lines; often the result of high-energy force
- spiral: complex, multi-planar fracture line; result of rotational force, low energy
- comminuted/multi-fragmentary: >2 fracture fragments
- intra-articular: fracture line crosses articular cartilage and enters joint
- compression: impaction of bone; typical sites are vertebrae or proximal tibia
- torus: compression of bony cortex on one side while the other remains intact, often seen in children (Figure 50)
- greenstick: compression of one side with fracture of the opposite cortex, often seen in children (Figure 50)
- pathologic: fracture through abnormal bone weakened by disease (e.g. tumour)



**Displacement**
Refers to position of the distal fragment relative to the proximal fragment



**Varus/Valgus Angulation**
Varus = Apex toward midline
Valgus = Apex away from midline



**Quick Motor Nerve Exam**
"Thumbs Up": PIN (Radial Nerve)
"OK Sign": AIN (Median Nerve)
"Spread Fingers": Ulnar Nerve



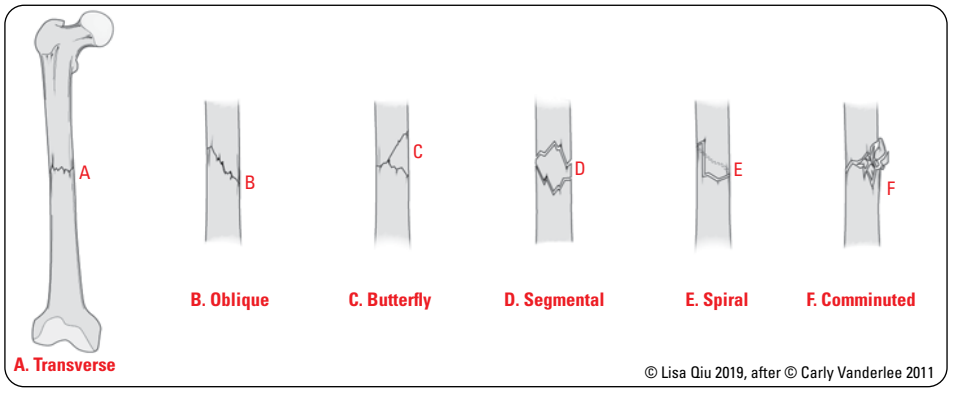
**X-Ray Rule of 2s**
2 sides = bilateral
2 views = AP + lateral
2 joints = joint above + below
2 times = before + after reduction



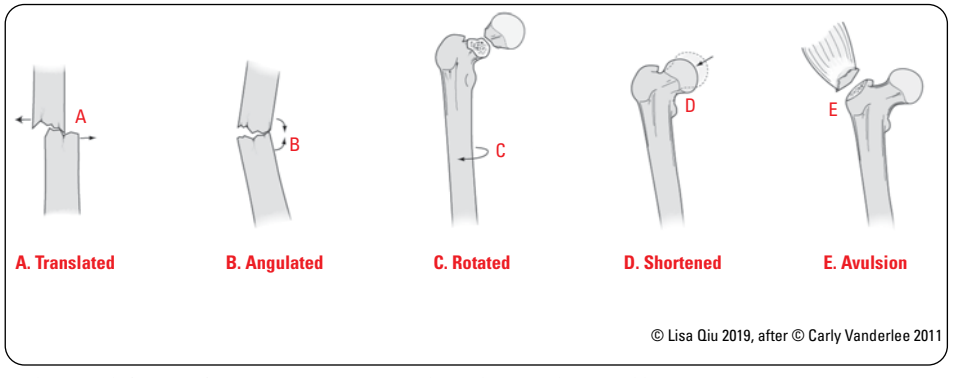
**Sample Fracture Description**
Closed (overlying skin integrity) spiral fracture (fracture pattern) of the distal third (location) of the left tibia (injured bone), with mild varus angulation, lateral translation and angulation (alignment of fracture fragments). The fracture does not extend to the joint surface

### 5. Alignment of Fracture Fragments (Figure 5)

- non-displaced: fracture fragments are in anatomic alignment
- displaced: fracture fragments are not in anatomic alignment
- distracted: fracture fragments are separated by a gap (opposite of impacted)
- translated: percentage of overlapping bone at fracture site
- angulated: direction of fracture apex (e.g. varus/valgus)




- rotated: fracture fragment rotated about long axis of bone




- shortened: fracture fragments are compressed, resulting in shortened bone
- avulsion: tendon or ligament tears/pulls off bone fragment

**Figure 4. Orientation/fracture pattern**
**Figure 5. Alignment of fracture fragments**

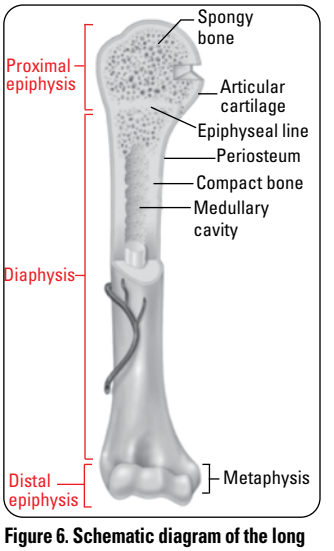



**Figure 6. Schematic diagram of the long bone**

# Approach to Fractures

### 1. Clinical Assessment

- ABCs, primary survey, and secondary survey (ATLS protocol)
  - assess for life threatening injury and other fractures
  - assess for open fracture
- **AMPLE- F** history (minimum): **A**llergies, **M**edications, **P**ast medical history, **L**ast meal, **E**vents (mechanism of injury), **F**unction pre-injury
  - previous significant injury or surgery to affected area
  - consider pathologic fracture with history of only minor trauma
- physical exam: inspect (deformity, soft tissue integrity); palpate (maximal tenderness, NVS- document best possible neurovascular exam, avoid ROM/moving injured area to prevent exacerbation)

### 2. Analgesia

- Oral, IV or local (e.g. hematoma block)

### 3. Imaging (see *Orthopedic X-Ray Imaging*, OR8)

### 4. Reduction: Closed vs. Open

- closed reduction (with IV sedation and muscle relaxation if necessary)
  - apply traction in the long axis of the limb
  - reverse the mechanism that produced the fracture
- open reduction
  - "NO CAST" (see sidebar)
  - other indications include
    - failed closed reduction
    - unable to cast or apply traction due to site
    - pathologic fractures
    - potential for improved function and/or outcomes with ORIF
- ALWAYS re-check and document NVS after reduction and obtain post-reduction x-ray

**Reasons for Closed Reduction and Splinting**

- Pain control
- Reduces further damage to vessels, nerves, and skin and may improve neurovascular status
- Reduces point loading on articular surfaces
- Decreases risk of inadvertently converting closed to open fracture
- Facilitates patient transport

**Indications for Open Reduction**

**NO CAST**
**N**on-union
**O**pen fracture
Neurovascular **C**ompromise
Displaced intra-**A**rticular fracture
**S**alter-Harris 3,4,5
Poly**T**rauma

**Buck's Skin Traction**
A system of weights, pulleys, and ropes that are attached to the end of a patient's bed exerting a longitudinal force on the distal end of a fracture, improving its length, alignment, and rotation temporarily while awaiting fixation (typically used for lower extremity fractures)

**5. Immobilization**
- external stabilization: splints, casts, traction, external fixator
- internal stabilization: percutaneous pinning, extramedullary fixation (screws, plates, wires), IM fixation (rods)

**6. Follow-Up**
- evaluate stages of bone healing (see *Fracture Healing*, OR10)

**7. Rehabilitation**
- recommend rehabilitation when appropriate to regain function and avoid joint stiffness

**Normal Healing**

| | |
|---|---|
| Weeks 0-3 | Hematoma, macrophages surround fracture site |
| Weeks 3-6 | Osteoclasts remove sharp edges, callus forms within hematoma |
| Weeks 6-12 | Bone forms within the callus, bridging fragments |
| Months 6-12 | Cortical gap is bridged by bone |
| Years 1-2 | Normal architecture is achieved through remodelling |

**Wolff's Law**
Bone adapts to the amount of force applied by increasing or decreasing its mass to resist the applied stress

# Fracture Healing

**Figure 7. Stages of bone healing**

## Evaluation of Healing: Tests of Union
- clinical: no longer tender to palpation or stressing on physical exam
- x-ray: trabeculae cross fracture site, visible callus bridging site on at least 3 of 4 cortices

**Fracture Blister**
Formation of vesicles or bullae that occur on edematous skin overlying a fractured bone

# General Fracture Complications

**Table 3. General Fracture Complications**

| | Early | Late |
|---|---|---|
| **Local** | Compartment syndrome<br>Neurological injury<br>Vascular injury<br>Infection<br>Implant failure<br>Fracture blisters | Mal-/non-union<br>AVN<br>Osteomyelitis<br>Heterotopic ossification<br>Post-traumatic OA<br>Joint stiffness/adhesive capsulitis<br>CRPS type I/RSD |
| **Systemic** | Sepsis<br>DVT<br>PE<br>ARDS secondary to fat embolism<br>Hemorrhagic shock | |

**Heterotopic Ossification**
The formation of bone in abnormal locations (e.g. in muscle), secondary to pathology

**CRPS/RSD**
An exaggerated response to an insult in the extremities; characterized by symptoms of hyperalgesia and allodynia, with signs of autonomic dysfunction (temperature asymmetry, mottling, hair or nail changes)

**Avascular Necrosis**
Ischemia of bone due to disrupted blood supply; most commonly affecting the femoral head, talus, or proximal scaphoid

# Articular Cartilage

## Properties
- hyaline cartilage
- 2-4 mm layer covering ends of articulating bones, provides nearly frictionless surface
- avascular (nutrition from synovial fluid), aneural, alymphatic

### ARTICULAR CARTILAGE DEFECTS

## Etiology
- overt trauma, repetitive minor trauma (such as repetitive ankle sprains or patellar maltracking)
- degenerative conditions such as early stage OA or osteochondritis dissecans

**Osteochondritis Dissecans**
Avascular necrosis of subchondral bone most often occurring in children and adolescents and causing pain and potentially hindering joint motion

## Clinical Features
- part of OA presentation: pain with movement, decreased range of motion, joint line pain with possible effusion
- have predisposing factors such as: ligament injury; malalignment of the joint (e.g. varus or valgus); obesity; AVN; and inflammatory arthropathy
- may have symptoms of locking or catching related to the torn/displaced cartilage

## Investigations
- X-ray (to rule out bony defects and check alignment)
- MRI (if X-ray is normal; MRI is not needed to assess cartilage loss associated with osteoarthritis)

**Table 4. Outerbridge Classification of Chondral Defects**

| Grade | Chondral Damage |
|---|---|
| I | Softening and swelling of cartilage |
| II | Fragmentation and fissuring <1/2" in diameter |
| III | Fragmentation and fissuring >1/2" in diameter |
| IV | Erosion of cartilage down to bone |

### Treatment
- individualized
  - patient factors (age, skeletal maturity, activity level, etc.)
  - defect factors (Outerbridge Classification, subchondral bone involvement, etc.)
- non-operative
  - rest, NSAIDs, bracing, physiotherapy
- operative
  - microfracture, osteochondral grafting (autograft or allograft), autologous chondrocyte implantation

# Orthopedic X-Ray Imaging

### General Principles - "Rule of 2s"
- x-ray 1 joint above and 1 below
- obtain at least 2 orthogonal views ± specialized views
- 2 sides, as needed for comparison

**Table 5. Orthopedic X-Ray Imaging**

| Site | Injury | X-Ray Views |
|---|---|---|
| **Shoulder** | Anterior dislocation<br>Posterior dislocation<br>AC | AP<br>Axillary ± stress view with 10 lb in hand<br>Trans-scapular<br>Zanca view (10-15 cephalic tilt) |
| **Arm** | Humerus # | AP<br>Lateral |
| **Elbow/Forearm** | Supracondylar #<br>Radial head #<br>Monteggia #<br>Night stick #<br>Galeazzi # | AP<br>Lateral |
| **Wrist** | Colles' #<br>Smith #<br>Scaphoid # | AP<br>Lateral<br>Clenched Fist (for scapholunate dissociation) |
| **Pelvis** | Pelvic # | AP pelvis<br>Inlet and outlet views<br>Judet views (obturator and iliac oblique for acetabular #) |
| **Hip** | Femoral head/neck #<br>Intertrochanteric #<br>Arthritis<br>SCFE<br>FAI | AP<br>Lateral<br>Frog-leg lateral<br>Dunn |
| **Knee** | Knee dislocation<br>Femur/tibia #<br>Patella #<br>Patella dislocation<br>Patella femoral syndrome | AP standing, lateral<br>Skyline – tangential view with knees flexed at 45° to see patellofemoral joint |
| **Leg** | Tibia shaft #<br>Fibula shaft # | AP<br>Lateral |
| **Ankle** | Ankle # | AP<br>Lateral<br>Mortise view: ankle at 15° of internal rotation |
| **Foot** | Talar #<br>Calcanial #<br>MT #<br>Lisfranc injuries | AP<br>Lateral<br>Oblique<br>Lateral Harris axial |
| **Spine** | Compression #<br>Burst #<br>Cervical spine # | AP spine<br>AP odontoid<br>Lateral<br>Oblique<br>Swimmer's view: lateral view with arm abducted 180° to evaluate C7-T1 junction if lateral view is inadequate<br>Lateral flexion/extension view: evaluate subluxation of cervical vertebrae |

# Orthopedic Emergencies

## Trauma Patient Workup

### Etiology
- high energy trauma e.g. MVC, fall from height
- may be associated with spinal injuries or life-threatening visceral injuries

### Clinical Features
- local swelling, tenderness, deformity of the limbs, and instability of the pelvis or spine
- decreased level of consciousness, hypotension, hypovolemia
- consider involvement of EtOH or other psychoactive substances

### Investigations
- trauma survey (see Emergency Medicine, ER7)
- x-rays: lateral cervical spine, AP chest, AP pelvis, AP and lateral of all bones suspected to be injured
- CT is also utilized to inspect for musculoskeletal injuries in the trauma setting
- other views of pelvis: AP, inlet, and outlet; Judet views for acetabular fracture (see *Classification of Pelvic Fractures* Table 19, OR28)

### Treatment
- ABCDEs and initiate resuscitation for life-threatening injuries
- assess genitourinary injury (rectal exam/vaginal exam mandatory)
- external or internal fixation of all fractures
- DVT prophylaxis

### Complications
- hemorrhage – life-threatening (may produce signs and symptoms of hypovolemic shock)
- fat embolism syndrome (SOB, hypoxemia, petechial rash, thrombocytopenia, and neurological symptoms)
- venous thrombosis – DVT and PE
- bladder/urethral/bowel injury
- neurological damage
- persistent pain/stiffness/limp/weakness in affected extremities
- post-traumatic OA of joints with intra-articular fractures
- sepsis if missed open fracture

## Open Fractures

- fractured bone and hematoma in communication with the external or contaminated environment

### Emergency Measures
- ABCs, primary survey, and resuscitation as needed
- removal of obvious foreign material
- irrigate with normal saline if grossly contaminated
- cover wound with sterile dressings
- immediate IV antibiotics
- tetanus toxoid or immunoglobulin as needed (see Plastic Surgery, PL10)
- NPO and prepare for OR (blood work, consent, ECG, CXR)
  - operative irrigation and debridement within 6-8 h to decrease risk of infection
  - ORIF
  - traumatic wound may be left open to drain with vacuum-assisted closure if necessary
  - re-examine with repeat irrigation and debridement in 48 h if necessary

**Table 6. Gustilo Classification of Open Fractures**

| Gustilo Grade | Length of Open Wound | Description | Prophylactic Antibiotic Regimen |
|---|---|---|---|
| I | <1 cm | Minimal contamination and soft tissue injury<br>Simple or minimally comminuted fracture | First generation cephalosporin (cefazolin) 2 g IV q8h for 2 d<br>If allergy use clindamycin 900 mg IV q8h<br>If MRSA positive use vancomycin 15 mg/kg IV q12h |
| II | 1-10 cm | Moderate contamination<br>Moderate soft tissue injury | As per Grade I |
| III* | >10 cm | IIIA: Extensive soft tissue injury with adequate ability of soft tissue to cover wound<br>IIIB: Extensive soft tissue injury with periosteal stripping and bone exposure; inadequate soft tissue to cover wound<br>IIIC: Vascular injury/compromise | First generation cephalosporin (cefazolin) for 2 d plus Gram-negative coverage (gentamicin or ceftriaxone) for at least 3 d<br>For soil or fecal contamination, metronidazole is added for anaerobic coverage ± penicillin G<br>If MRSA positive use vancomycin 15 mg/kg IV q12h |

*Any high energy, comminuted fracture, shot gun, farmyard/soil/water contamination, exposure to oral flora, or fracture >8 h old is immediately classified as Grade III

**Orthopedic Emergencies**

**VON CHOP**
**V**ascular compromise
**O**pen fracture
**N**eurological compromise/cauda equina syndrome
**C**ompartment syndrome
**H**ip dislocation
**O**steomyelitis/septic arthritis
Unstable **P**elvic fracture

**Controversies in Initial Management of Open Fractures**
Scand J Surg 2014;103(2):132-7
**Study**: Literature review examining the initial management of open fractures. 40 studies included.
**Findings:**
- A first-generation cephalosporin (or clindamycin) should be administered upon arrival. In general, 24 h of antibiotics after each debridement is sufficient to reduce infection rates.
- Although cultures are taken from delayed (>24 h) or infected injuries, it may not be necessary to routinely take post-debridement cultures in open fractures.
- Open fractures should be debrided as soon as possible, although the "6 h rule" is not generally valid.
- Wounds should be closed within 7 d once soft tissue has stabilized and all non-viable tissue removed.
- Negative pressure wound therapy (NPWT) has been shown to decrease infection rates in open fractures.

33% of patients with open fractures have multiple injuries

**Antibiotics for Preventing Infection in Open Limb Fractures**
Cochrane DB Syst Rev 2004;1:CD003764
**Purpose**: To review the evidence regarding the effectiveness of antibiotics in the initial treatment of open fractures of the limbs.
**Methods**: Randomized or quasi-randomized controlled trials comparing antibiotic treatment with placebo or no treatment in preventing acute wound infection were identified and reviewed. Data were extracted and pooled for analysis.
**Results**: Eight studies (n=1106) were reviewed. The use of antibiotics had a protective effect against early infection compared with no antibiotics or placebo (RRR=0.43, 95% CI 0.29, 0.65; ARR=0.07, 95% CI 0.03–0.10).
**Conclusions**: Antibiotics reduce the incidence of early infections in open fractures of the limbs.

# Cauda Equina Syndrome

- see Neurosurgery, NS27

# Compartment Syndrome

- increased interstitial pressure in an anatomical compartment (forearm, calf) where muscle and tissue are bounded by fascia and bone (fibro-osseous compartment), with little room for expansion
- interstitial pressure exceeds capillary perfusion pressure, leading to muscle necrosis (in 4-6 h) and eventually nerve necrosis

## Etiology

- intracompartmental
  - fracture (particularly tibial shaft or paediatric supracondylar and forearm fractures)
  - reperfusion injury, crush injury, or ischemia
- extracompartmental: constrictive dressing (circumferential cast), poor position during surgery, circumferential burn

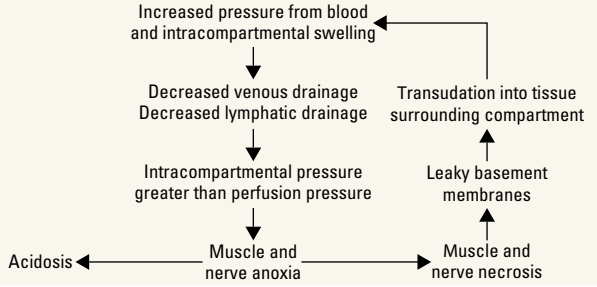



**Figure 8. Pathogenesis of compartment syndrome**

## Clinical Features

- pain out of proportion to injury (typically first symptom and the most significant finding)
- pain with active contraction of compartment
- pain with passive stretch (most sensitive)
- swollen, tense compartment
- suspicious history

- **5 Ps:** late sign – do not wait for these to develop to make the diagnosis!

Most important sign is increased pain with passive stretch. Most important symptom is pain out of proportion to injury

**5 Ps of Compartment Syndrome**
**P**ain: out of proportion for injury and not relieved by analgesics
- Increased pain with passive stretch of compartment muscles

**P**allor: late finding
**P**aresthesia
**P**aralysis: late finding
**P**ulselessness: late finding

## Investigations

- usually not necessary, as compartment syndrome is a clinical diagnosis
- in children or unconscious patients where clinical exam is unreliable, compartment pressure monitoring with catheter (normal = 0 mmHg; elevated ≥30 mmHg or [measured pressure – dBP] ≤30 mmHg)

## Treatment

- non-operative
  - remove constrictive dressings (casts, splints), elevate limb at the level of the heart
- operative
  - urgent fasciotomy
  - 48-72 h post-operative: necrotic tissue debridement + wound closure
  - may require delayed closure and/or skin grafting

## Complications

- Volkmann's ischemic contracture: ischemic necrosis of muscle; followed by secondary fibrosis; and finally calcification - especially following supracondylar fracture of humerus
- rhabdomyolysis, renal failure secondary to myoglobinuria

# Osteomyelitis

- bone infection with progressive inflammatory destruction

## Etiology

- most commonly caused by *S. aureus*
- mechanism of spread: hematogenous (most common) vs. direct-inoculation vs. contiguous focus
- risk factors: recent trauma/surgery, immunocompromised patients, DM, IV drug use, poor vascular supply, peripheral neuropathy

**Plain Film Findings of Osteomyelitis**
- Soft tissue swelling
- Lytic bone destruction*
- Periosteal reaction (formation of new bone, especially in response to #)*

*Generally not seen on plain films until 10-12 d after onset of infection

### Clinical Features
- symptoms: pain and fever
- on exam: erythema, tenderness, edema common ± abscess/draining sinus tract; impaired function/WB

### Diagnosis
- see Medical Imaging, MI23
- workup includes: WBC and differential, ESR, CRP, blood culture, aspirate culture/bone biopsy

**Table 7. Treatment of Osteomyelitis**

| Acute Osteomyelitis | Chronic Osteomyelitis |
|---|---|
| IV antibiotics 4-6 wk; started empirically and adjusted after obtaining blood and aspirate cultures | Surgical debridement |
| ± surgery (I&D) for abscess or significant involvement | Antibiotics: both local (e.g. antibiotic beads) and systemic (IV) |
| ± hardware removal (if present) | |

Rapid progression of signs and symptoms (over hours) necessitates need for serial examinations

Acute osteomyelitis is a medical emergency which requires an early diagnosis and appropriate antimicrobial and surgical treatment

## Septic Joint

- joint infection with progressive destruction if left untreated

### Etiology
- most commonly caused by *S. aureus* in adults
- consider coagulase-negative Staphylococcus in patients with prior joint replacement
- consider *N. gonorrhoeae* in sexually active adults and newborns
- most common route of infection is hematogenous
- risk factors: young/elderly (age >80 yr), prosthetic joint, recent joint surgery, skin infection/ulcer, IV drug use, recent intra-articular corticosteroid injection, immunocompromised (cancer, DM, alcoholism, RA)

### Clinical Features
- inability/refusal to bear weight, localized joint pain, erythema, warmth, swelling, pain on active and passive ROM, ± fever

### Investigations
- X-ray (to rule out fracture, tumour, metabolic bone disease), ESR, CRP, WBC, blood cultures
- joint aspirate: cloudy yellow fluid, WBC >50,000 with >90% neutrophils, protein level >4.4 mg/dL, joint glucose level <60% blood glucose level, no crystals, positive Gram stain results
- listen for heart murmur (re: concern for infective endocarditis, use Duke Criteria)

### Treatment
- IV antibiotics, empiric therapy (based on age and risk factors), adjust following joint aspirate C&S results
- non-operative
  - therapeutic joint aspiration, serially if necessary
- operative
  - arthroscopic/open irrigation and drainage

Most commonly affected joints in descending order
knee → hip → elbow → ankle → sternoclavicular joint

**Plain Film Findings in a Septic Joint**
- Early (0-3 d): usually normal; may show soft-tissue swelling or joint space widening from localized edema
- Late (4-6 d): joint space narrowing and destruction of cartilage

Serial C-reactive protein (CRP) can be used to monitor response to therapy

**Does This Adult Patient Have Septic Arthritis?**
JAMA 2007;297(13):1478-88
**Purpose**: To review the accuracy and precision of the clinical evaluation for the diagnosis of nongonococcal bacterial arthritis.
**Methods**: Review of 14 studies including 6242 patients of which 653 had positive synovial culture (gold standard diagnostic tool for septic arthritis).
**Results/Conclusions**: Age, diabetes mellitus, rheumatoid arthritis, joint surgery, hip or knee prosthesis, skin infection, and human immunodeficiency virus type 1 infection significantly increase the probability of septic arthritis. Joint pain, history of joint swelling, and fever are useful clinical findings in identifying patients with a monoarticular arthritis who may have septic arthritis. Laboratory findings from an arthrocentesis are also required and helpful prior to Gram stain and culture. The presence of increased WBC increases the likelihood ratio (for counts <25 000/μL: LR, 0.32; 95% CI, 0.23-0.43; for counts ≥25 000/μL: LR, 2.9; 95% CI, 2.5-3.4; for counts ≥100 000/μL: LR, 28.0; 95% CI, 12.0-66.0). A polymorphonuclear cell count of ≥90% increases the LR of septic arthritis by 3.4, while a PMN cell count of <90% reduces the LR by 0.34.

# Shoulder

## Shoulder Dislocation

- complete loss of continuity between the two articular surfaces of the glenohumeral joint; may be anterior or posterior

### Investigations
- anterior dislocation X-rays: AP, trans-scapular, and axillary views of the shoulder
- posterior dislocation X-rays: AP, trans-scapular, and axillary views of the shoulder; or CT scan

**Posterior Shoulder Dislocation**
Up to 60-80% are missed on initial presentation due to poor physical exam and radiographs

**There are 4 Joints in the Shoulder**
Glenohumeral, AC, sternoclavicular (SC), scapulothoracic

## Table 8. Anterior and Posterior Shoulder Dislocation

| | Anterior Shoulder Dislocation (>90%) | Posterior Shoulder Dislocation (5%) |
|---|---|---|
| **MECHANISM** | | |
| | Abducted arm is externally rotated/hyperextended<br>Blow to posterior shoulder<br>Involuntary, usually traumatic; voluntary, atraumatic | Adducted, internally rotated, flexed arm<br>FOOSH<br>3 Es (epileptic seizure, EtOH, electrocution)<br>Blow to anterior shoulder |
| **CLINICAL FEATURES** | | |
| **Symptoms** | Pain, arm slightly abducted and externally rotated with inability to internally rotate | Pain, arm is held in adduction and internal rotation; external rotation is blocked |
| **Shoulder Exam** | **"Squared off" shoulder**<br>**Positive apprehension test**: patient looks apprehensive with gentle shoulder abduction and external rotation to 90° as humeral head is pushed anteriorly and recreates feeling of anterior dislocation<br>**Positive relocation test**: a posteriorly directed force applied during the apprehension test relieves apprehension since anterior subluxation is prevented<br>**Positive sulcus sign**: presence of subacromial indentation with distal traction on humerus indicates inferior shoulder instability | **Anterior shoulder flattening**, prominent coracoid, palpable mass posterior to shoulder<br>**Positive posterior apprehension ("jerk") test**: with patient supine, flex elbow 90° and adduct, internally rotate the arm while applying a posterior force to the shoulder; patient will "jerk" back with the sensation of subluxation<br>Note: the posterior apprehension test is used to test for recurrent posterior instability, NOT for acute injury |
| **Neurovascular Exam Including** | Axillary nerve: sensory patch over deltoid and deltoid contraction<br>Musculocutaneous nerve: sensory patch on lateral forearm and biceps contraction | Full neurovascular exam as per anterior shoulder dislocation |
| **RADIOGRAPHIC FINDINGS** | | |
| **Axillary View** | Humeral head is anterior | Humeral head is posterior |
| **Trans-scapular 'Y' View** | Humeral head is anterior to the centre of the "Mercedes-Benz" sign | Humeral head is posterior to centre of "Mercedes-Benz" sign |
| **AP View** | Sub-coracoid lie of the humeral head is most common | Partial vacancy of glenoid fossa (vacant glenoid sign) and >6 mm space between anterior glenoid rim and humeral head (positive rim sign), humeral head may resemble a lightbulb due to internal rotation (lightbulb sign) |
| **Hill-Sachs and Bony Bankart Lesions** | ± Hill-Sachs lesion: compression fracture of posterior humeral head due to forceful impaction of an anteriorly dislocated humeral head against the glenoid rim<br>± bony Bankart lesion: avulsion of the anterior glenoid labrum (with attached bone fragments) from the glenoid rim | ± **Reverse Hill-Sachs lesion** (75% of cases): divot in anterior humeral head<br>± **Reverse bony Bankart lesion**: avulsion of the posterior glenoid labrum from the bony glenoid rim |
| **TREATMENT** | | |
| | Closed reduction with IV sedation and muscle relaxation<br>**Traction-countertraction**: assistant stabilizes torso with a folded sheet wrapped across the chest while the surgeon applies gentle steady traction<br>**Stimson:** while patient lies prone with arm hanging over table edge, hang a 5 lb weight on wrist for 15-20 min<br>**Hippocratic method**: place heel into patient's axilla and apply traction to arm<br>**Cunningham's method**: low risk, low pain; if not successful try above methods<br>Obtain post-reduction x-rays<br>Check post-reduction NVS<br>Sling x 3 wk (avoid abduction and external rotation), followed by shoulder rehabilitation (dynamic stabilizer strengthening) | Closed reduction with sedation and muscle relaxation<br>Inferior traction on a flexed elbow with pressure on the back of the humeral head<br>Obtain post-reduction x-rays<br>Check post-reduction NVS<br>Sling in abduction and external rotation x 3 wk, followed by shoulder rehabilitation (dynamic stabilizer strengthening) |

## Prognosis

- recurrence rate depends on age of first dislocation
- <20 yr = 65-95%; 20-40 yr = 60-70%; >40 yr = 2-4%

## Specific Complications

- recurrent/unreduced dislocation (most common complication)
- rotator cuff or capsular or labral tear (Bankart/SLAP lesion), shoulder stiffness
- injury to axillary nerve/artery, brachial plexus

**Shoulder passive ROM**: abduction – 180°, adduction – 45°, flexion – 180°, extension – 45°, int. rotation – level of T4, ext. rotation – 40-45°

**Factors Causing Shoulder Instability**

- Shallow glenoid
- Loose capsule
- Ligamentous laxity

**Frequency of Dislocations**

- Anterior shoulder > Posterior shoulder
- Posterior hip > Anterior hip

The glenohumeral joint is the most commonly dislocated joint in the body since stability is sacrificed for motion

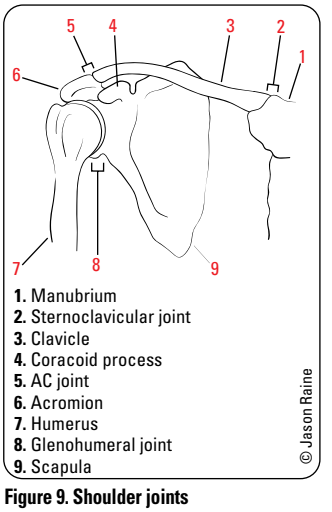



**Figure 9. Shoulder joints**

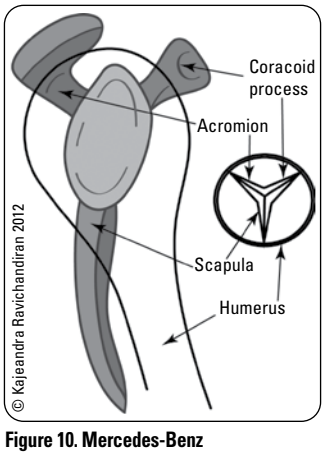



**Figure 10. Mercedes-Benz**

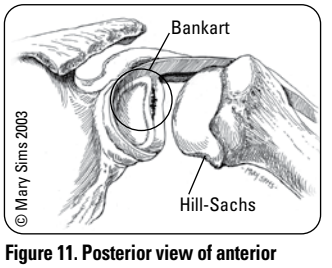
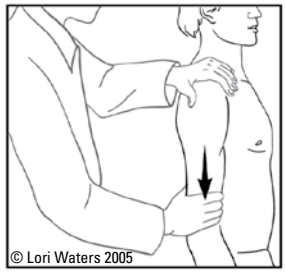


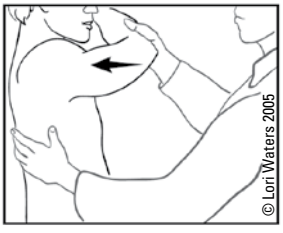

**Figure 11. Posterior view of anterior dislocation causing Hill-Sachs and Bankart lesions**



Anterior apprehension sign



Sulcus sign



Posterior apprehension sign



Traction-Countertraction

**Figure 12. Shoulder maneuvers**

# Rotator Cuff Disease

- rotator cuff consists of 4 muscles that act to stabilize the humeral head within the glenoid fossa

**Table 9. Rotator Cuff Muscles (SITS)**

| Muscle | Muscle Attachments | | Nerve Supply | Muscle Function |
|---|---|---|---|---|
| | Proximal | Distal | | |
| **Supraspinatus** | Scapula | Greater tuberosity of humerus | Suprascapular nerve | Abduction |
| **Infraspinatus** | Scapula | Greater tuberosity of humerus | Suprascapular nerve | External rotation |
| **Teres Minor** | Scapula | Greater tuberosity of humerus | Axillary nerve | External rotation |
| **Subscapularis** | Scapula | Lesser tuberosity of humerus | Subscapular nerve | Internal rotation and adduction |

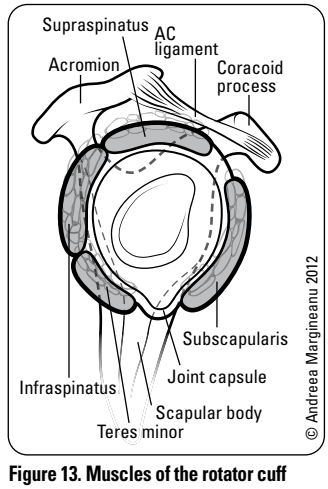



**Figure 13. Muscles of the rotator cuff**

## SPECTRUM OF DISEASE: IMPINGEMENT, TENDONITIS, MICRO OR MACRO TEARS

### Etiology

- anything that leads to a narrow subacromial space
- most commonly, a relative imbalance of rotator cuff and larger shoulder muscles, allowing for superior translation and subsequent wear of the rotator cuff muscle tendons
  - glenohumeral muscle weakness leading to abnormal motion of humeral head
  - scapular muscle weakness leading to abnormal motion of acromion
- acromial abnormalities, such as congenital narrow space or osteophyte formation or Type III acromion morphology
  1. outlet/subacromial impingement: "painful arc syndrome", compression of rotator cuff tendons (primarily supraspinatus) and subacromial bursa between the head of the humerus and the undersurface of acromion, AC joint, and CA ligament
  2. bursitis and tendonitis
  3. rotator cuff thinning and tear if left untreated

### Clinical Features

- insidious onset, but may present as an acute exacerbation of chronic disease, night pain, and difficulty sleeping on affected side
- pain worsens with active motion (especially overhead); passive movement generally permitted
- weakness and loss of ROM, especially between 90°-130° (e.g. trouble with overhead activities)
- tenderness to palpation over greater tuberosity
- rule out bicep tendinosis: Speed's test; SLAP lesion: O'Brien's test

### Investigations

- X-ray: AP view may show high riding humerus relative to glenoid, indicating large tear, evidence of chronic tendonitis
- MRI: coronal/sagittal, oblique and axial orientations are useful for assessing full/partial tears and tendinopathy ± arthrogram: geyser sign (injected dye leaks out of joint through rotator cuff tear)
- arthrogram: can assess full thickness tears, difficult to assess partial tears

**Bigliani Classification of Acromion Morphology**
- Type I – flat
- Type II – curved
- Type III – hooked

**Screening Out Rotator Cuff Tears***
- No night pain (SN 87.7%)
- No painful arc (SN 97.5%)
- No impingement signs (SN 97.2%)
- No weakness

*Returning to the bedside: Using the history and physical examination to identify rotator cuff tears
JAM Geri Soc 2000;48:1633-7

## Treatment

- non-operative
  - mild or moderate cases
  - physiotherapy, NSAIDs ± steroid injection
  - all rotator cuff injury treatment begins with physiotherapy (regardless of severity on MRI findings), with progression to surgery if necessary
- operative
  - severe tear or impingement that is refractory to 2-3 mo physiotherapy and 1-2 corticosteroid injections
  - arthroscopic or open surgical repair (i.e. acromioplasty, rotator cuff repair)

**Ruling in Rotator Cuff Tears – 98% probability of rotator cuff tear if all** 3 of the following are present:
- Supraspinatus weakness
- External rotation weakness
- Positive impingement sign(s)

Diagnosis of rotator cuff tears.
Lancet 2001; 357:769-70

**Does this Patient with Shoulder Pain have Rotator Cuff Disease? The Rational Clinical Examination Systematic Review**
JAMA 2013;310:837-847
**Study**: 5 studies of sufficient quality including 30-203 shoulders and a prevalence of RCD ranging from 33-81%.
**Results/Conclusions**: Among pain provocation tests, a positive painful arc test had the greatest specificity and sensitivity (SP 81%, SN 71%). Among strength tests, a positive external rotation lag test and internal rotation lag test were the most accurate for full-thickness tears (SP 47%, SN 94%; SP 97%, SN 83% respectively). The internal rotation lag test was therefore also the most accurate for identifying patients without a full-thickness tear.
A positive drop arm test is helpful to identify patients with RCD (SN 24%, SP 93%).

### Table 10. Rotator Cuff Special Tests

| Test | Examination | Positive Test |
|---|---|---|
| **Jobe's Test (i.e. Empty Can Test)** | Supraspinatus: place the shoulder in 90° of abduction and 30° of forward flexion and internally rotate the arm so that the thumb is pointing toward the floor | Weakness with active resistance suggests a supraspinatus tear |
| **Lift-off Test** | Subscapularis: internally rotate arm so dorsal surface of hand rests on lower back; patient instructed to actively lift hand away from back against examiner resistance (use Belly Press Test if too painful) | Inability to actively lift hand away from back suggests a subscapularis tear |
| **Posterior-Cuff Test** | Infraspinatus and teres minor: arm positioned at patient's side in 90° of flexion; patient instructed to externally rotate arm against the resistance of the examiner | Weakness with active resistance suggests posterior cuff tear |
| **Neer's Test** | Rotator cuff impingement: passive shoulder flexion | Pain elicited between 130-170° suggests impingement |
| **Hawkins-Kennedy Test** | Rotator cuff impingement: shoulder flexion to 90° and passive internal rotation | Pain with internal rotation suggests impingement |
| **Painful Arc Test** | Rotator cuff tendinopathy: patient instructed to actively abduct the shoulder | Pain with abduction >90° suggests tendinopathy |
| **Speed's Test** | Apply resistance to the forearm when the arm is in forward flexion with the elbows fully extended. | Pain in the bicipital groove |
| **O'Brien's Test** | SLAP lesion: forward flexion of the arm to 90 degrees while keeping the arm extended. Arm is adducted 10-15 degrees. Internally rotate the arm so thumb is facing down and apply a downward force. Repeat the test with arm externally rotated | Pain or clicking in the glenohumoral joint in internal rotation but not external rotation |

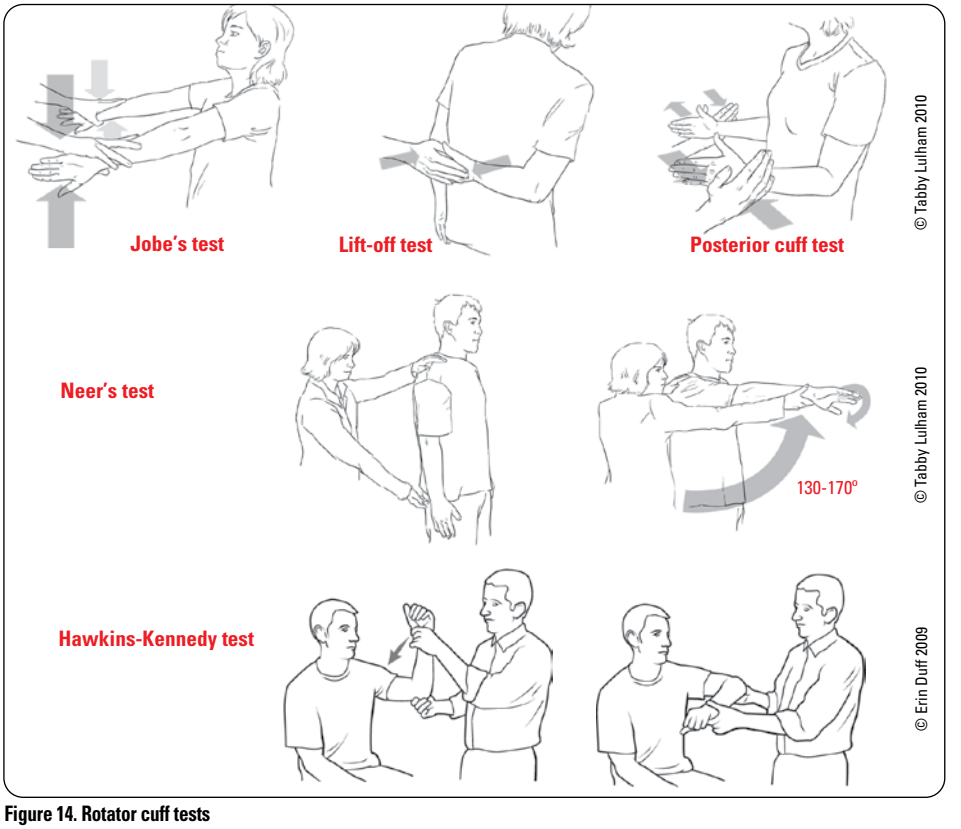



**Figure 14. Rotator cuff tests**

# Acromioclavicular Joint Pathology

- subluxation or dislocation of AC joint
- 2 main ligaments attach clavicle to scapula: AC and CC ligaments

### Mechanism
- fall onto shoulder with adducted arm or direct trauma to point of shoulder

### Clinical Features
- pain with adduction of shoulder and/or palpation over AC joint
- palpable step deformity between distal clavicle and acromion (with dislocation) i.e. piano key sign
- limited ROM

### Investigations
- X-rays: bilateral AP, Zanca view (10-15° cephalic tilt), axillary

### Treatment
- non-operative
  - sling 1-3 wk, ice, analgesia, early ROM and rehabilitation
- operative
  - indication: Rockwood Class IV-VI (III if labourer or high level athlete)
  - number of different approaches involving AC/CC ligament reconstruction or screw/hook plate insertion



Pneumothorax or pulmonary contusion are potential complications of severe clavicle fracture, and rarely severe AC joint dislocation

**Table 11. Rockwood Classification of Acromioclavicular Joint Separation**

| Grade | Features | Treatment |
|---|---|---|
| I | Joint sprain, absence of complete tear of either ligament | Non-operative |
| II | Complete tear of AC ligament, incomplete tear of CC ligament, without marked elevation of lateral clavicular head | Non-operative |
| III | Complete tear of AC and CC ligaments, >5 mm elevation at AC joint, superior aspect of acromion is below the inferior aspect of the clavicle | Most non-operative, operative if labourer or high level athlete<br>Will heal with step deformity, although most fully functional in 4-6 mo |
| IV-VI | Based on the anatomical structure the displaced clavicle is in proximity to | Operative in most cases |

| Grade | AC Ligament | CC Ligament | Reducible | Treatment |
|---|---|---|---|---|
| I | Sprained | Normal | N/A | Non-operative |
| II | Torn | Sprained | Yes | Non-operative |
| III | Torn | Torn | Yes | Most non-operative, operative if labourer or high-level athlete<br>Will heal with step deformity, although most fully functional in 4-6 mo |
| IV-VI | Torn | Torn | No | Operative in most cases |

Rockwood separations IV-VI are determined based on direction of displacement:
IV: Distal clavicle displaced posteriorly into trapezius (seen on axillary XR)
V: Distal clavicle herniated through deltotrapezial fascia into subcutaneous tissue
VI: Distal clavicle displaced inferior to acromion or coracoid under conjoined tendon (rare)

# Clavicle Fracture

- incidence: proximal (5%), middle (80%), or distal (15%) third of clavicle
- common in children (unites rapidly without complications)

### Mechanism
- fall on shoulder (87%), direct trauma to clavicle (7%), FOOSH (6%)

### Clinical Features
- pain and tenting of skin
- arm is clasped to chest to splint shoulder and prevent movement

### Investigations
- evaluate NVS of entire upper limb
- X-ray: AP, 45° cephalic tilt (superior/inferior displacement), 45° caudal tilt (AP displacement)
- CT: useful for medial physeal fractures and sternoclavicular injury



**Non-Operative Treatment Compared with Plate Fixation of Displaced Mid-Shaft Clavicular Fractures. A Multicentre, Randomized Clinical Trial**
J Bone Joint Surg. Am. 2007; 89(1),1-10
**Purpose**: To compare non-operative treatment with plate fixation in displaced mid-shaft clavicular fractures.
**Results**: Constant shoulder scores and DASH scores were significantly improved in the operative fixation group at all time-points ($p = 0.001$ and $p < 0.01$, respectively). The mean time to radiographic union was 28.4 weeks in the non-operative group compared with 16.4 weeks in the operative group ($p = 0.001$). At one year after the injury, the patients in the operative group were more likely to be satisfied with the appearance of the shoulder ($p = 0.001$) and with the shoulder in general ($p = 0.002$) than were those in the non-operative group.
**Conclusions**: Operative fixation of a displaced fracture of the clavicular shaft results in improved functional outcome and a lower rate of malunion and nonunion compared with non-operative treatment at one year of follow-up.

### Treatment
- medial and middle-third clavicle fractures
  - for nondisplaced fractures, simple sling x 1-2 wk prn
  - early ROM and strengthening once pain subsides
  - if fracture is shortened >2 cm, consider ORIF
- distal-third clavicle fractures
  - undisplaced (with ligaments intact): sling x 1-2 wk
  - displaced (CC ligament injury): ORIF

**Associated Injuries with Clavicle Fractures**
- Up to 9% of clavicle fractures are associated with other fractures (most commonly rib fractures)
- Majority of brachial plexus injuries are associated with proximal third fractures

### Specific Complications (see *General Fracture Complications*, OR7)
- cosmetic bump usually only complication
- shoulder stiffness, weakness with repetitive activity
- pneumothorax, brachial plexus injuries, and subclavian vessel (all very rare)

## Frozen Shoulder (Adhesive Capsulitis)

- disorder characterized by progressive pain and stiffness of the shoulder, usually resolving spontaneously after 18 mo

### Mechanism
- primary adhesive capsulitis
  - idiopathic, often associated with DM
  - usually resolves spontaneously in 9-18 mo
- secondary adhesive capsulitis
  - due to prolonged immobilization
  - shoulder-hand syndrome: CRPS/RSD characterized by arm and shoulder pain, decreased motion, and diffuse swelling
  - following MI, stroke, shoulder trauma
  - poorer outcomes

**Conditions Associated with an Increased Incidence of Adhesive Capsulitis**
- Prolonged immobilization (most significant)
- Female gender
- Age >49 yr
- DM (5x)
- Cervical disc disease
- Hyperthyroidism
- Stroke
- MI
- Trauma and surgery
- Autoimmune disease

### Clinical Features
- gradual onset (weeks to months) of diffuse shoulder pain with:
  - decreased active AND passive ROM
  - pain worse at night and often prevents sleeping on affected side
  - increased stiffness as pain subsides: continues for 6-12 mo after pain has disappeared

**Stages of Adhesive Capsulitis**
1. Freezing phase: gradual onset, diffuse pain (lasts 6-9 mo)
2. Frozen phase: decreased ROM impacts function (lasts 4-9 mo)
3. Thawing phase: gradual return of motion (lasts 5-26 mo)

### Investigations
- X-ray: AP (neutral, internal/external rotation), scapular Y, and axillary views of the shoulder
  - may be normal, or may show demineralization from disease

### Treatment
- freezing phase
  - active and passive ROM (physiotherapy)
    - NSAIDs and steroid injections if limited by pain
- thawing phase
  - manipulation under anesthesia and early physiotherapy
    - arthroscopy for debridement/decompression

# Humerus

## Proximal Humeral Fracture

### Mechanism
- young: high energy trauma (MVC)
- elderly: FOOSH from standing height in osteoporotic individuals

### Clinical Features
- proximal humeral tenderness, deformity with severe fracture, swelling, painful ROM, bruising extends down arm and chest

### Investigations
- test axillary nerve function (deltoid contraction and skin over deltoid)
- X-rays: AP, trans-scapular, and axillary views of the shoulder are essential
- CT scan: to evaluate for articular involvement and fracture displacement

### Classification
- Neer classification is based on 4 fracture locations or 'parts'
- displaced: displacement >1 cm and/or angulation >45°
- the Neer system regards the number of displaced fractures, not the fracture line, in determining classification
- ± dislocated/subluxed: humeral head dislocated/subluxed from glenoid

**Neer Classification**
**Based on 4 parts of humerus**
- Greater Tuberosity
- Lesser Tuberosity
- Humeral Head
- Shaft

**One-part fracture**: any of the 4 parts with none displaced
**Two-part fracture**: any of the 4 parts with 1 displaced
**Three-part fracture**: displaced fracture of surgical neck + displaced greater tuberosity or lesser tuberosity
**Four-part fracture**: displaced fracture of surgical neck + both tuberosities

### Treatment
- assess for and treat osteoporosis if needed
- non-operative
  - nondisplaced and minimally displaced (85% of patients): broad arm sling immobilization, begin ROM within 14 d to prevent stiffness
  - most displaced fractures in low-demand elderly patients
- operative
  - ORIF (anatomic neck fractures, displaced, associated irreducible glenohumeral joint dislocation)
  - hemiarthroplasty or reverse TSA may be necessary, especially in elderly

### Specific Complications (see *General Fracture Complications*, OR7)
- AVN, nerve palsy (45%; typically axillary nerve), malunion, post-traumatic arthritis, persistent pain and weakness, frozen shoulder

## Humeral Shaft Fracture

### Mechanism
- high energy: direct blows/MVC (especially young); low energy: FOOSH, twisting injuries, metastases (in elderly)

### Clinical Features
- pain, swelling, weakness ± shortening, motion/crepitus at fracture site
- must test radial nerve function before and after treatment: look for drop wrist, sensory impairment in dorsum of hand

### Investigations
- X-ray: AP and lateral views of the humerus, including the shoulder and elbow joints

### Treatment
- in general, humeral shaft fractures are treated non-operatively
- non-operative
  - ± reduction; can accept deformity due to compensatory ROM of shoulder
  - hanging cast (weight of arm in cast provides traction across fracture site) with collar and cuff sling immobilization until swelling subsides, then Sarmiento functional brace, followed by ROM
- operative
  - indications: see *"NO CAST"* OR6, pathological fracture, "floating elbow" (simultaneous unstable humeral and forearm fractures)
  - ORIF: plating (most common), IM rod insertion, external fixation

### Specific Complications (see *General Fracture Complications*, OR7)
- radial nerve palsy: expect spontaneous recovery in 3-4 mo, otherwise send for EMG
- non-union: most frequently seen in middle 1/3
- decreased ROM
- compartment syndrome

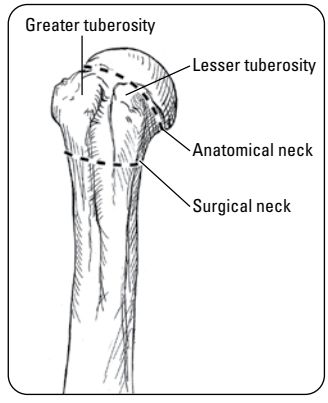



**Figure 15. Fractures of the proximal humerus**

**Acceptable Humeral Shaft Deformities for Non-Operative Treatment**
- <20° anterior angulation
- <30° varus angulation
- <3 cm of shortening

Risk of radial nerve and brachial artery injury

## Distal Humeral Fracture

### Mechanism
- young: high energy trauma (MVC)
- elderly: FOOSH

### Clinical Features
- elbow pain and swelling
- assess brachial artery

### Investigations
- X-ray: AP and lateral views of the humerus and elbow
- CT scan: helpful when suspecting shear fracture of capitulum or trochlea
- assess NVS: radial, ulnar and median nerve

### Classification
- supracondylar, distal single column, distal bicolumnar, and coronal shear fractures

### Treatment
- goal is to restore ROM to 30-130° flexion (unsatisfactory outcomes in 25%)
- non-operative (pediatric patients only)
  - cast immobilization (in supination for lateral condyle fracture; pronation for medial condyle fractures)
- operative
  - indications: displaced, supracondylar, bicolumnar
  - closed reduction and percutaneous pinning (children); ORIF; total elbow arthroplasty (bicolumnar in elderly)
  - adult fractures are almost always treated operatively due to risk of elbow stiffness with non-operative management

The anterior humeral line refers to an imaginary line drawn along the anterior surface of the humeral cortex that passes through the middle third of the capitellum when extended inferiorly. In subtle supracondylar fractures, the anterior humeral line is disrupted, typically passing through the anterior third of the capitellum

# Elbow

## Supracondylar Fracture

- subclass of distal humerus fracture: extra-articular, fracture proximal to capitulum and trochlea, usually transverse
- most common in pediatric population (peak age ~7 yr old), rarely seen in adults
- AIN (median nerve) injury commonly associated with extension type

### Mechanism
- >96% are extension injuries via FOOSH (e.g. fall off monkey bars); <4% are flexion injuries

### Clinical Features
- pain, swelling, point tenderness
- neurovascular injury: median and radial nerves, radial artery

### Investigations
- X-ray: AP and lateral views of the elbow
  - disruption of anterior humeral line suggests supracondylar fracture
  - fat pad sign: a sign of effusion and can be indicative of occult fracture
  - assess NVS: median and radial nerves, radial artery

### Treatment
- non-operative
  - nondisplaced (pediatric): long arm plaster slab in 90° flexion x 3 wk
- operative
  - indications: displaced >50%, vascular injury, open fracture
  - requires percutaneous pinning followed by limb cast with elbow flexed <90°
  - in adults, ORIF is necessary

### Specific Complications (see *General Fracture Complications*, OR7)
- stiffness is most common
- brachial artery injury (kinking can occur if displaced fracture), median or ulnar nerve injury, compartment syndrome (leads to Volkmann's ischemic contracture), malalignment cubitus varus (distal fragment tilted into varus)

**Three Joints at the Elbow**
- Humeroradial joint
- Humeroulnar joint
- Radioulnar joint

Normal carrying angle of elbow is ~10° of valgus

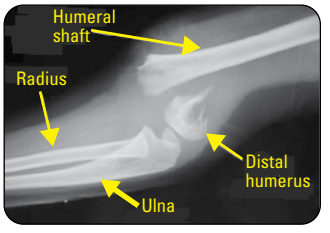



**Figure 16. X-ray of transverse displaced supracondylar fracture of humerus with elbow dislocation**

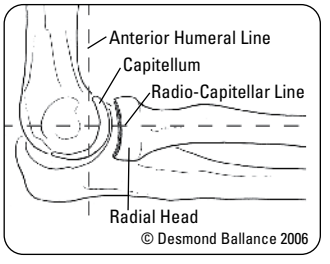



**Figure 17. Lateral view of elbow**

## Radial Head Fracture

- a common fracture of the upper limb in young adults

### Mechanism
- FOOSH with elbow extended and forearm pronated

### Clinical Features
- marked local tenderness on palpation over radial head (lateral elbow)
- decreased ROM at elbow, ± mechanical block to forearm pronation and supination
- pain on pronation/supination

### Investigations (Figure 18)
- X-ray: AP and lateral views of the elbow
  - enlarged anterior fat pad ("sail sign") or the presence of a posterior fat pad on lateral view indicates effusion, which could occur with occult radial head fractures

**Table 12. Classification and Treatment of Radial Head Fractures**

| Mason Class | Radiographic Description | Treatment |
|---|---|---|
| 1 | Nondisplaced fracture | Elbow slab or sling x 3-5 d with early ROM |
| 2 | Displaced fracture | ORIF if: angulation >30°, involves ≥1/3 of the radial head, or if ≥3 mm of joint incongruity exists |
| 3 | Comminuted fracture | Radial head excision ± prosthesis (if ORIF not feasible) |
| 4 | Comminuted fracture with posterior elbow dislocation | Radial head excision ± prosthesis |

### Specific Complications (see *General Fracture Complications*, OR7)
- myositis ossificans – calcification of muscle
- recurrent instability (if MCL injured and radial head excised)

**Terrible Triad**
- Radial head fracture
- Coronoid fracture
- Elbow dislocation

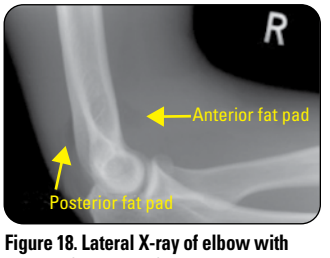



**Figure 18. Lateral X-ray of elbow with effusion ("sail sign")**

To avoid stiffness, do not immobilize elbow joint >2-3 wk

# Olecranon Fracture

### Mechanism
- direct trauma to posterior aspect of elbow (fall onto the point of the elbow) or FOOSH

### Clinical Features
- localized pain, palpable defect
- ± loss of active extension due to avulsion of triceps tendon

### Investigations
- X-ray: AP and lateral (require true lateral to determine fracture pattern)

### Treatment
- non-operative
  - non-displaced (<2 mm, stable): cast x 2-3 wk (elbow in 90° flexion), then gentle ROM
- operative
  - displaced: ORIF (plate and screws or tension-band wiring) and early ROM if stable

# Elbow Dislocation

- third most common joint dislocation after shoulder and patella
- anterior capsule and collateral ligaments disrupted



**Elbow Dislocation**
The radio-capitellar line refers to an imaginary line along the longitudinal axis of the radial neck that passes through the centre of the capitellum, regardless of the degree of elbow flexion. If the radio-capitellar line does not pass through the centre of the capitellum a dislocation should be suspected

### Mechanism
- elbow hyperextension via FOOSH or valgus/supination stress during elbow flexion
- usually the radius and ulna are dislocated together, alternatively the radial head dislocates in isolation and the ulna is fractured ("Monteggia Fracture")
- 80% are posterior/posterolateral, anterior are rare and usually devastating

### Clinical Features
- elbow pain, swelling, deformity
- flexion contracture
- ± absent radial or ulnar pulses

### Investigations
- X-ray: AP and lateral views of the elbow
- assess NVS: brachial artery, median and ulnar nerves

### Treatment
- non-operative
  - closed reduction under conscious sedation (post-reduction x-rays required)
  - Parvin's method: patient lies prone with arm hanging down; apply gentle traction downwards on wrist; as olecranon slips distally, gently lift up the arm at elbow to reduce joint
  - long-arm splint with forearm in neutral rotation and elbow in 90° flexion
  - early ROM (<2 wk)
- operative
  - indications: complex dislocation or persistent instability after closed reduction
  - ORIF

### Specific Complications (see *General Fracture Complications*, OR7)
- stiffness (loss of extension), intra-articular loose body, neurovascular injury (ulnar nerve, median nerve, brachial artery), radial head fracture
- recurrent instability uncommon

# Epicondylitis

- lateral epicondylitis = "tennis elbow", inflammation of the common extensor tendon as it inserts into the lateral epicondyle
- medial epicondylitis = "golfer's elbow", inflammation of the common flexor tendon as it inserts into the medial epicondyle



**T**ennis Elbow = la**T**eral epicondylitis; pain associated with ex**T**ension of wrist

### Mechanism
- repeated or sustained contraction of the forearm muscles/chronic overuse

### Clinical Features
- point tenderness over humeral epicondyle and/or distal to it
- pain upon resisted wrist extension (lateral epicondylitis) or wrist flexion (medial epicondylitis)
- generally a self-limited condition, but may take 6-18 mo to resolve

### Treatment
- non-operative (very good outcomes)
  - rest, ice, NSAIDs
  - use brace/strap
  - physiotherapy, stretching, and strengthening
  - corticosteroid injection
- operative
  - indication: failed 6-12 mo conservative therapy
  - percutaneous or open release of common tendon from epicondyle

**Elbow Joint Injection**
Inject at the centre of the triangle formed by the lateral epicondyle, radial head, and olecranon

# Forearm

## Radius and Ulna Shaft Fractures

### Mechanism
- high-energy direct or indirect (MVA, fall from height, sports) trauma
- fractures usually accompanied by displacement due to high force

### Clinical Features
- deformity, pain, swelling
- loss of function in hand and forearm

### Investigations
- X-ray: AP and lateral of forearm ± oblique of elbow and wrist
- CT if fracture is close to joint

### Treatment
- goal is anatomic reduction since imperfect alignment significantly limits forearm pronation and supination
- ORIF with plates and screws; closed reduction with immobilization usually yields poor results for displaced forearm fractures (except in children)

### Specific Complications (see *General Fracture Complications*, OR7)
- soft tissue contracture resulting in limited forearm rotation – surgical release of tissue may be warranted

## Monteggia Fracture

- fracture of the proximal ulna with radial head dislocation and proximal radioulnar joint injury
- more common and better prognosis in the pediatric age group when compared to adults

### Mechanism
- direct blow to the posterior aspect of the forearm
- hyperpronation
- fall on the hyperextended elbow

### Clinical Features
- pain, swelling, decreased rotation of forearm ± palpable lump at the radial head
- ulna angled apex anterior and radial head dislocated anteriorly (rarely the reverse deformity occurs)

### Investigations
- X-ray: AP and lateral views of the elbow, wrist and forearm

### Treatment
- adults: ORIF of ulna with indirect reduction of radiocapitellar joint in 90% of patients (open reduction of radiocapitellar joint if unsuccessful)
- splint and early post-operative ROM if elbow completely stable, otherwise immobilization in plaster with elbow flexed for 2-3 wk
- pediatrics: attempt closed reduction and immobilization in plaster with elbow flexed for Bado Type I-III, surgery for Type IV

### Specific Complications (see *General Fracture Complications*, OR7)
- PIN injury: most common nerve injury; observe for 3 mo as most resolve spontaneously
- radial head instability/redislocation
- radioulnar synostosis

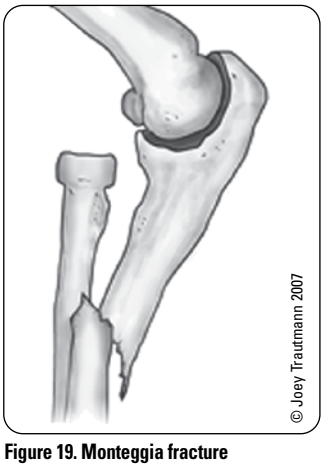


**Figure 19. Monteggia fracture**

In all isolated ulna fractures, assess proximal radius to rule out a Monteggia fracture

**Bado Type Classification of Monteggia Fractures**
Based on the direction of displacement of the dislocated radial head, generally the same direction as the apex of the ulnar fracture
Type I: anterior dislocation of radial head and proximal/middle third ulnar fracture (60%)
Type II: posterior dislocation of radial head and proximal/middle third ulnar fracture (15%)
Type III: lateral dislocation of radial head and metaphyseal ulnar fracture (20%)
Type IV – combined: proximal fracture of the ulna and radius, dislocation of the radial head in any direction (<5%)

## Nightstick Fracture

- isolated fracture of ulna without dislocation of radial head

### Mechanism
- direct blow to forearm (e.g. holding arm up to protect face)

### Treatment
- non-operative
  - indication: non-displaced
  - below elbow cast (x 10 d), followed by forearm brace (~8 wk)
- operative
  - indication: significantly displaced
  - ORIF if >50% shaft displacement or >10° angulation

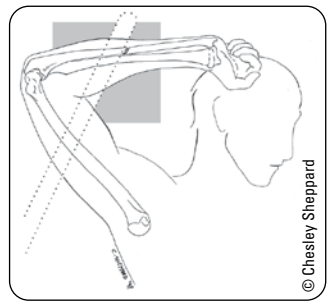



**Figure 20. Nightstick fracture**

## Galeazzi Fracture

- fracture of the distal radial shaft with disruption of the DRUJ
- most commonly in the distal 1/3 of radius near junction of metaphysis/diaphysis

### Mechanism
- hand FOOSH with axial loading of pronated forearm or direct wrist trauma

### Clinical Features
- pain, swelling, deformity, and point tenderness at fracture site

### Investigations
- X-ray: AP, and lateral views of the elbow, wrist, and forearm
  - shortening of distal radius >5 mm relative to the distal ulna
  - widening of the DRUJ space on AP
  - dislocation of radius with respect to ulna on true lateral

### Treatment
- all cases are operative
  - ORIF of radius; afterwards, assess DRUJ stability by balloting distal ulna relative to distal radius
  - if DRUJ is stable and reducible, splint for 10-14 d with early ROM encouraged
  - if DRUJ is unstable, ORIF or percutaneous pinning with long arm cast in supination x 2-3 wk

For all isolated radius fractures assess DRUJ to rule out a Galeazzi fracture

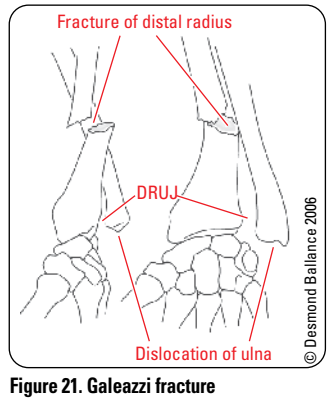



**Figure 21. Galeazzi fracture**

# Wrist

## Colles' Fracture

- extra-articular transverse distal radius fracture (~2 cm proximal to the radiocarpal joint) with dorsal displacement ± ulnar styloid fracture
- most common fracture in those >40 yr, especially in women and those with osteoporotic bone

### Mechanism
- FOOSH

### Clinical Features
- "dinner fork" deformity
- swelling, ecchymosis, tenderness

### Investigations
- X-ray: AP and lateral views of the wrist

### Treatment
- goal is to restore radial height (13 mm), radial inclination (22°), volar tilt (11°), as well as DRUJ stability and useful forearm rotation
- non-operative
  - closed reduction (think opposite of the deformity)
  - hematoma block (sterile prep and drape, local anesthetic injection directly into fracture site) or conscious sedation
  - closed reduction: traction with extension (exaggerate injury); traction with ulnar deviation, pronation, flexion (of distal fragment – not at wrist)
  - dorsal slab/below elbow cast for 5-6 wk
  - obtain post-reduction films immediately; repeat reduction if necessary
  - x-ray at 1 wk, 3 wk, and at cessation of immobilization to ensure reduction is maintained

**Indications for Direct Surgical Management of Colles' Fracture**
- Displaced intra-articular fracture
- Comminuted
- Severe osteoporosis
- Dorsal angulation >5° or volar tilt >20°
- >5 mm radial shortening

**Features of Inadequate Closed Reduction that Require ORIF**
- Radial shortening >3 mm or,
- Dorsal tilt >10° or,
- Intra-articular displacement/step-off >2 mm

- operative
  - indication: failed closed reduction, or loss of reduction
  - percutaneous pinning, external fixation, or ORIF

# Smith's Fracture

- volar displacement of the distal radius (i.e. reverse Colles' fracture)

### Mechanism
- fall onto the back of the flexed hand

### Investigations
- X-ray: AP and lateral views of the wrist

### Treatment
- usually unstable and needs ORIF
- if patient is poor operative candidate, may attempt non-operative treatment
  - closed reduction with hematoma block (reduction opposite of Colles')
  - long-arm cast in supination x 6 wk

# Complications of Wrist Fractures

- most common complications are poor grip strength, stiffness, and radial shortening
- distal radius fractures in individuals <40 yr of age are usually highly comminuted and are more likely to require ORIF
- 80% have normal function in 6-12 mo

**Table 13. Early and Late Complications of Wrist Fractures**

| Early | Late |
|---|---|
| Difficult reduction ± loss of reduction | Malunion, radial shortening |
| Compartment syndrome | Painful wrist secondary to ulnar prominence |
| Extensor pollicis longus tendon rupture | Frozen shoulder ("shoulder-hand syndrome") |
| Acute carpal tunnel syndrome | Post-traumatic arthritis |
| Finger swelling with venous block | Carpal tunnel syndrome |
| Complications of a tight cast/splint | CRPS/RSD |

# Scaphoid Fracture

### Epidemiology
- most common carpal bone injured
- common in young men; not common in children or in patients beyond middle age
- may be associated with other carpal or wrist injuries (e.g. Colles' fracture)

### Mechanism
- FOOSH: impaction of scaphoid on distal radius, most commonly resulting in a transverse fracture through the waist (65%), distal (10%), or proximal (25%) scaphoid

### Clinical Features
- pain with resisted pronation
- tenderness in the anatomical "snuff box", over scaphoid tubercle, and pain with long axis compression into scaphoid
- usually nondisplaced

### Investigations
- X-ray: AP, lateral, and scaphoid views with wrist extension and ulnar deviation
- ± CT or MRI: detect occult fracture and prevent AVN
- bone scan rarely used
  - note: a fracture may not be radiologically evident up to 2 wk after acute injury, so if a patient complains of wrist pain and has anatomical snuff box tenderness but a negative x-ray, treat as if positive for a scaphoid fracture and repeat x-ray 2 wk later to rule out a fracture; if x-ray still negative, order CT or MRI

### Treatment
- early treatment critical for improving outcomes
- non-operative
  - non-displaced (<1 mm displacement/<15° angulation): long-arm thumb spica cast x 4 wk, then short arm cast until radiographic evidence of healing is seen (2-3 mo)
- operative
  - displaced: ORIF with headless/countersink compression screw is the mainstay treatment

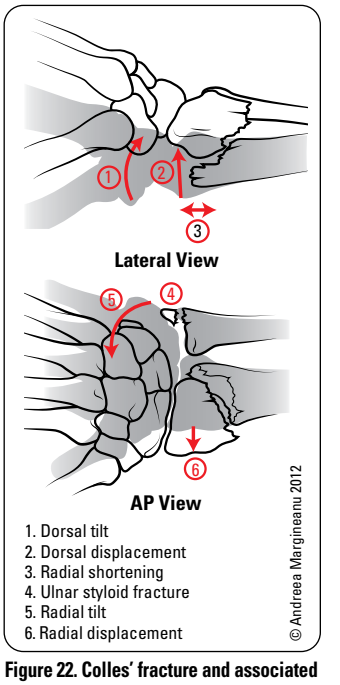



**Figure 22. Colles' fracture and associated bony deformity**

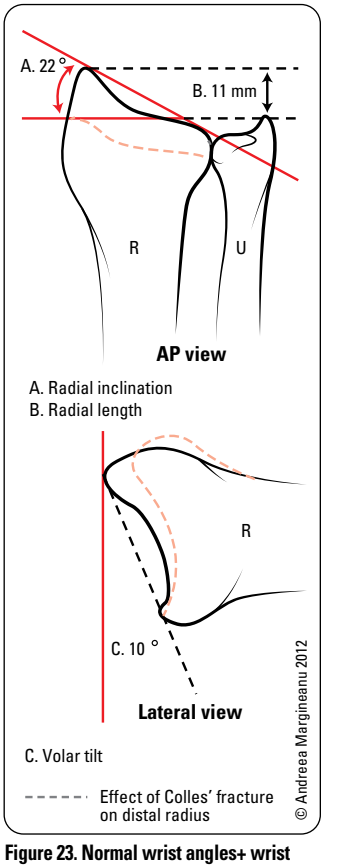



**Figure 23. Normal wrist angles+ wrist angles in Colles' fracture**
Note the relative shortening of the radius relative to the ulna on AP view in Colles' fracture

**Scaphoid Fracture Special Tests**
Tender snuff box: 100% sensitivity, but 29% specific, as it is also positive with many other injuries of radial aspect of wrist with FOOSH

### Specific Complications (see *General Fracture Complications*, OR7)
- most common: nonunion/malunion (use bone graft from iliac crest or distal radius with fixation to heal)
- AVN of the proximal fragment
- delayed union (recommend surgical fixation)
- scaphoid nonunion advanced collapse (SNAC) – chronic nonunion leading to advanced collapse and arthritis of wrist

### Prognosis
- proximal fifth fracture: AVN rate 100%; proximal third fracture: AVN rate 33%
- waist fractures have healing rates of 80-90%
- distal third fractures have healing rates close to 100%

The proximal pole of the scaphoid receives as much as 100% of its arterial blood supply from the radial artery that enters at the distal pole. A fracture through the proximal third disrupts this blood supply and results in a high incidence of AVN/nonunion

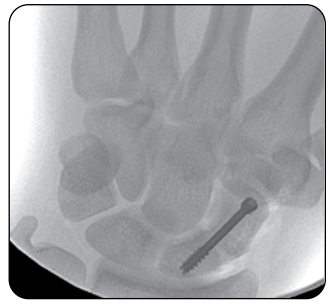


**Figure 24. ORIF left scaphoid**

# Hand

- see Plastic Surgery, PL23

# Spine

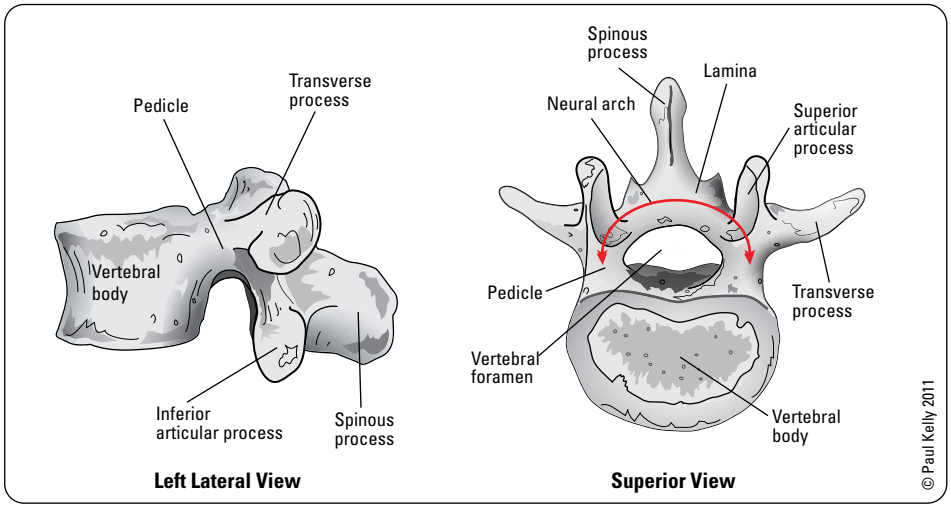



**Figure 27. Schematic diagram of vertebral anatomy**
Adapted from: Moore KL, Agur AMR. Essential Clinical Anatomy, 3rd ed. Philadephia: Lippincott Williams and Wilkins, 2007. p274

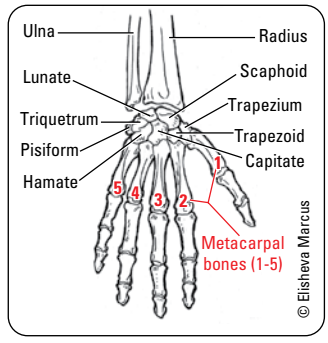



**Figure 25. Carpal bones**

## Fractures of the Spine

- see Neurosurgery, NS34

## Cervical Spine

### General Principles
- C1 (atlas): no vertebral body, no spinous process
- C2 (axis): odontoid = dens
- 7 cervical vertebrae; 8 cervical nerve roots
- nerve root exits above vertebra (i.e. C4 nerve root exits above C4 vertebra), C8 nerve root exits below C7 vertebra
- radiculopathy = impingement of nerve root
- myelopathy = impingement of spinal cord

### Special Testing
- compression test: pressure on head worsens radicular pain
- distraction test: traction on head relieves radicular symptoms
- Valsalva test: Valsalva maneuver increases intrathecal pressure and causes radicular pain

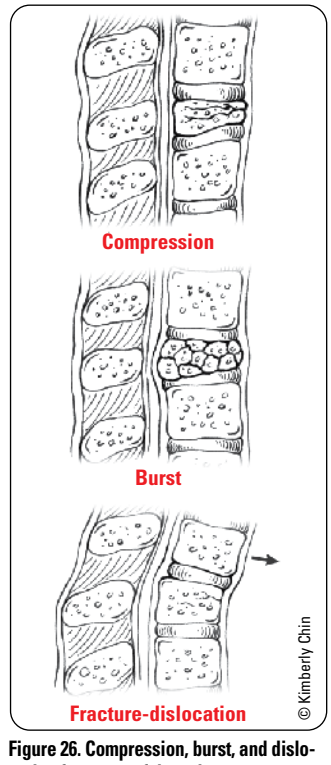



**Figure 26. Compression, burst, and dislocation fractures of the spine**

**Table 14. Cervical Radiculopathy/Neuropathy**

| Root | C5 | C6 | C7 | C8 |
|---|---|---|---|---|
| **Motor** | Deltoid<br>Biceps<br>Wrist extension | Biceps<br>Brachioradialis | Triceps<br>Wrist flexion<br>Finger extension | Interossei<br>Digital flexors |
| **Sensory** | Axillary nerve (patch over lateral deltoid) | Thumb | Index and middle finger | Ring and little finger |
| **Reflex** | Biceps | Biceps<br>Brachioradialis | Triceps | Finger jerk |

### X-Rays for C-Spine
- AP spine: alignment
- AP odontoid: atlantoaxial articulation
- lateral
  - vertebral alignment: posterior vertebral bodies should be aligned (translation >3.5 mm is abnormal)
  - angulation: between adjacent vertebral bodies (>11° is abnormal)
  - disc or facet joint widening
  - anterior soft tissue space (at C3 should be ≤3 mm; at C4 should be ≤8-10 mm)
- oblique: evaluate pedicles and intervertebral foramen
- ± swimmer's view: lateral view with arm abducted 180° to evaluate C7-T1 junction if lateral view is inadequate
- ± lateral flexion/extension view: evaluate subluxation of cervical vertebrae

### Differential Diagnosis of C-Spine Pain
- neck muscle strain, cervical spondylosis, cervical stenosis, RA (spondylitis), traumatic injury, whiplash, myofascial pain syndrome, acute discogenic nerve root entrapment, infection, fracture, neoplasm, pain from soft tissue structure

### C-SPINE INJURY
- see Neurosurgery, NS34

## Thoracolumbar Spine

### General Principles
- spinal cord terminates at conus medullaris (L1/2)
- individual nerve roots exit below pedicle of vertebra (i.e. L4 nerve root exits below L4 pedicle)

### Special Tests
- **straight leg raise**: passive lifting of leg (30-70°) reproduces radicular symptoms of pain radiating down posterior/lateral leg to knee ± into foot
- **Lasegue maneuver**: dorsiflexion of foot during straight leg raise makes symptoms worse, or if leg is less elevated, dorsiflexion will bring on symptoms
- **femoral stretch test**: with patient prone, flexing the knee of the affected side and passively extending the hip results in radicular symptoms of unilateral pain in anterior thigh

**Table 15. Lumbar Radiculopathy/Neuropathy**

| Root | L4 | L5 | S1 |
|---|---|---|---|
| **Motor** | Quadriceps (knee extension + hip adduction)<br>Tibialis anterior (ankle inversion + dorsiflexion) | Extensor hallucis longus<br>Gluteus medius (hip abduction) | Peroneus longus + brevis (ankle eversion)<br>Gastrocnemius + soleus (plantar flexion) |
| **Sensory** | Medial malleolus | 1st dorsal webspace and lateral leg | Lateral foot |
| **Screening Test** | Squat and rise | Heel walking | Walking on toes |
| **Reflex** | Knee (patellar) | Medial hamstring* | Ankle (Achilles) |
| **Test** | Femoral stretch | Straight leg raise | Straight leg raise |

*Unreliable

### Differential Diagnosis of Back Pain
1. mechanical or nerve compression (>90%)
   - degenerative (disc, facet, ligament)
   - peripheral nerve compression (disc herniation)
   - spinal stenosis (congenital, osteophyte, central disc)
   - cauda equina syndrome
2. others (<10%)
   - neoplastic (primary, metastatic, multiple myeloma)
   - infectious (osteomyelitis, TB)
   - metabolic (osteoporosis)
   - traumatic fracture (compression, distraction, translation, rotation)
   - spondyloarthropathies (ankylosing spondylitis)
   - referred (aorta, renal, ureter, pancreas)

## DEGENERATIVE DISC DISEASE

- loss of vertebral disc height with age resulting in:
  - bulging and tears of annulus fibrosus
  - change in alignment of facet joints
  - osteophyte formation

### Mechanism

- compression over time with age

### Clinical Features

- axial back pain without radicular symptoms
- pain worse with axial loading and flexion
- negative straight leg raise

### Investigations

- X-ray, MRI, provocative discography

### Treatment

- non-operative
  - staying active with modified activity
  - back strengthening
  - NSAIDs
  - **do NOT treat with opioids**; no proven efficacy of spinal traction or manipulation
- operative – rarely indicated
  - decompression ± fusion
  - no difference in outcome between non-operative and surgical management at 2 yr

## SPINAL STENOSIS

- narrowing of spinal canal <10 mm
- congenital (idiopathic, osteopetrosis, achondroplasia) or acquired (degenerative, iatrogenic – post spinal surgery, ankylosing spondylosis, Paget's disease, trauma)

### Clinical Features

- ± bilateral back and leg pain
- neurogenic claudication
- ± motor weakness
- normal back flexion; difficulty with back extension (Kemp sign)
- positive straight leg raise, pain not worse with Valsalva

### Investigations

- CT/MRI reveals narrowing of spinal canal, but gold standard = CT myelogram

### Treatment

- non-operative
  - vigorous physiotherapy (flexion exercises, stretch/strength exercises), NSAIDs, lumbar epidural steroids
- operative
  - indication: non-operative failure >6 mo
  - decompressive surgery

**Table 16. Differentiating Claudication**

| | Neurogenic | Vascular |
|---|---|---|
| **Aggravation** | With standing or exercise<br>Walking distance variable | Walking set distance |
| **Alleviation** | Change in position (usually flexion, sitting, lying down) | Stop walking |
| **Time** | Relief in ~10 min | Relief in ~2 min |
| **Character** | Neurogenic ± neurological deficit | Muscular cramping |

## MECHANICAL BACK PAIN

- back pain NOT due to prolapsed disc or any other clearly defined pathology

### Clinical Features

- dull backache aggravated by activity and prolonged standing
- morning stiffness
- no neurological signs

### Treatment

- symptomatic (analgesics, physiotherapy)
- prognosis: symptoms may resolve in 4-6 wk, others become chronic



Cauda equina syndrome and ruptured aortic aneurysms are causes of low back pain that are considered surgical emergencies

## LUMBAR DISC HERNIATION

- tear in annulus fibrosus allows protrusion of nucleus pulposus, causing either a central, posterolateral, or lateral disc herniation, most commonly at L5-S1 > L4-5 > L3-4
- 3:1 male to female
- only 5% become symptomatic
- usually a history of flexion-type injury

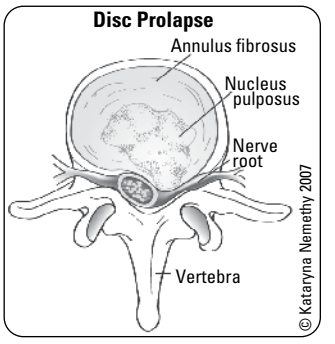



**Figure 28. Disc herniation causing nerve root compression**

### Clinical Features

- back dominant pain (central herniation) or leg dominant pain (lateral herniation)
- tenderness between spinous processes at affected level
- muscle spasm ± loss of normal lumbar lordosis
- neurological disturbance is segmental and varies with level of central herniation
  - motor weakness (L4, L5, S1)
  - diminished reflexes (L4, S1)
  - diminished sensation (L4, L5, S1)
- positive straight leg raise
- positive contralateral SLR
- positive Lasegue and Bowstring sign
- cauda equina syndrome (present in 1-10%): surgical emergency

### Investigations

- X-ray, MRI, consider a post-void residual volume to check for urinary retention; post-void >100 mL should heighten suspicion for cauda equina syndrome

Neurogenic claudication is position dependent; vascular claudication is exercise dependent

### Treatment

- non-operative
  - symptomatic
    - extension protocol
    - NSAIDS
- operative
  - indication: progressive neurological deficit, failure of symptoms to resolve within 3 mo, or cauda equina syndrome due to central disc herniation
  - surgical discectomy
- prognosis
  - 90% of patients improve in 3 mo with non-operative treatment

MRI abnormalities (e.g. spinal stenosis, disc herniation) are quite common in both asymptomatic and symptomatic individuals and are not necessarily an indication for intervention without clinical correlation

**Table 17. Types of Low Back Pain**

| | Mechanical Back Pain | | Direct Nerve Root Compression | |
|---|---|---|---|---|
| | **Disc Origin** | **Facet Origin** | **Spinal Stenosis** | **Root Compression** |
| **Pain Dominance** | Back | Back | Leg | Leg |
| **Aggravation** | Flexion | Extension, standing, walking | Exercise, extension, walking, standing | Flexion |
| **Onset** | Gradual | More sudden | Congenital or acquired | Acute leg ± back pain |
| **Duration** | Long (weeks, months) | Shorter (days, weeks) | Acute or chronic history (weeks to months) | Short episodes Attacks (minutes) |
| **Treatment** | Relief of strain, exercise | Relief of strain, exercise | Relief of strain, exercise + surgical decompression if progressive or severe deficit | Relief of strain, exercise + surgical decompression if progressive or severe deficit |

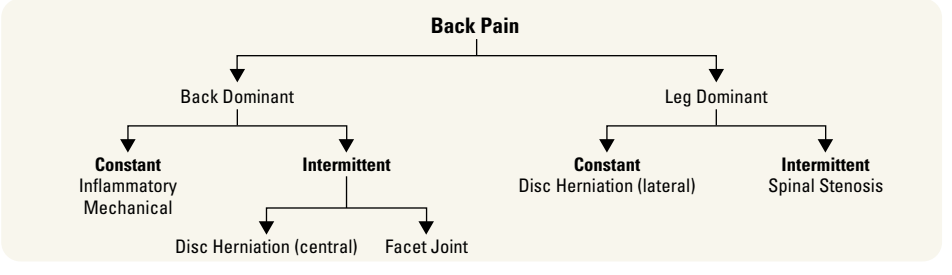



**Figure 29. Approach to back pain**

**Red Flags for**

**BACK PAIN**
**B**owel or bladder dysfunction
**A**nesthesia (saddle)
**C**onstitutional symptoms/malignancy
**K**hronic disease
**P**aresthesias
**A**ge >50 yr
**I**V drug use
**N**euromotor deficits

## SPONDYLOLYSIS

### Definition

- defect in the pars interarticularis with no movement of the vertebral bodies

### Mechanism

- trauma: gymnasts, weightlifters, backpackers, loggers, labourers

**Sciatica**

- Most common symptom of radiculopathy (L4-S3)
- Leg dominant, constant, burning pain
- Pain radiates down leg ± foot
- Most common cause = disc herniation

### Clinical Features
- activity-related back pain, pain with unilateral extension (Michelis' test)

### Investigations
- oblique X-ray: "collar" break in the "Scottie dog's" neck
- bone scan
- CT scan

### Treatment
- non-operative
  - activity restriction, brace, stretching exercise

## ADULT ISTHMIC SPONDYLOLISTHESIS

### Definition
- defect in pars interarticularis causing a forward translation or slippage of one vertebra on another, usually at L5-S1, less commonly at L4-5

### Mechanism
- congenital (children), degenerative (adults), traumatic, pathological, teratogenic

### Clinical Features
- lower back pain radiating to buttocks relieved with sitting
- neurogenic claudication
- L5 radiculopathy
- Meyerding Classification (percentage of slip)

### Investigations
- X-ray (AP, lateral, oblique flexion-extension views), MRI

### Treatment
- non-operative
  - activity restriction, bracing, NSAIDS
- operative

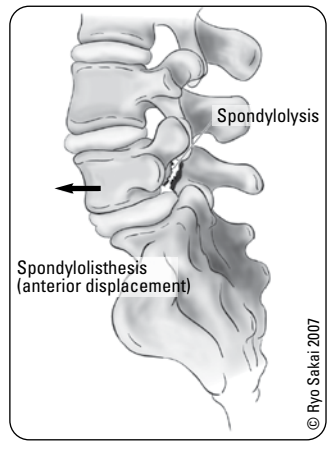



**Figure 30. Spondylolysis, spondylolisthesis**

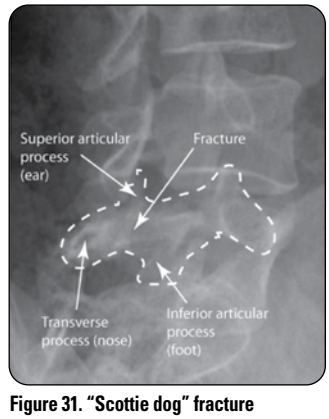



**Figure 31. "Scottie dog" fracture**

**Table 18. Classification and Treatment of Spondylolisthesis**

| Class | Percentage of Slip | Treatment |
|---|---|---|
| 1 | 0-25% | Symptomatic operative fusion only for intractable pain |
| 2 | 25-50 | Same as above |
| 3 | 50-75 | Decompression for spondylolisthesis and spinal fusion |
| 4 | 75-100 | Same as above |
| 5 | >100 | Same as above |

### Specific Complications
- may present as cauda equina syndrome due to roots being stretched over the edge of L5 or sacrum

# Pelvis

## Pelvic Fracture

### Mechanism
- young: high energy trauma, either direct or by force transmitted longitudinally through the femur
- elderly: fall from standing height, low energy trauma
- lateral compression, vertical shear, or anteroposterior compression fractures

### Clinical Features
- pain, inability to bear weight
- local swelling, tenderness
- deformity of lower extremity
- pelvic instability

### Investigations
- X-ray: AP pelvis, inlet and outlet views, Judet views (obturator and iliac oblique for acetabular fracture)
  - 6 cardinal radiographic lines of the acetabulum: ilioischial line, iliopectineal line, teardrop, roof, posterior rim, anterior rim
- CT scan useful for evaluating posterior pelvic injury and acetabular fracture
- assess genitourinary injury (rectal exam, vaginal exam, hematuria, blood at urethral meatus)
  - if involved, the fracture is considered an open fracture

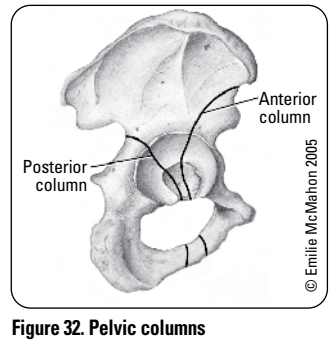



**Figure 32. Pelvic columns**

### Classification

**Table 19. Tile Classification of Pelvic Fractures**

| Type | Stability | Description |
|---|---|---|
| **A** | Rotationally stable<br>Vertically stable | A1: fracture not involving pelvic ring (i.e. avulsion or iliac wing fracture)<br>A2: minimally displaced fracture of pelvic ring (e.g. ramus fracture)<br>A3: transverse sacral fracture |
| **B** | Rotationally unstable<br>Vertically stable | B1: open book (external rotation)<br>B2: lateral compression – ipsilateral<br>B2-1: with anterior ring rotation/displacement through ipsilateral rami<br>B2-2: with anterior ring rotation/displacement through non-ipsilateral rami (bucket-handle)<br>B3: bilateral |
| **C** | Rotationally unstable<br>Vertically unstable | C1: unilateral<br>C1-1: iliac fracture, C1-2: sacroiliac fracture-dislocation<br>C1-3: sacral fracture<br>C2: bilateral with 1 side type B and 1 side type C<br>C3: bilateral both sides type C |

**Possible Radiological Findings**
- Pubic rami fractures: superior/inferior
- Pubic symphysis diastasis: common in AP compression (N=5 mm)
- Sacral fractures: common in lateral compression
- SI joint diastasis: common in AP compression (N=1-4 mm)
- Disrupted anterior column (iliopectineal line) or posterior column (ilioischial line)
- "Teardrop" displacement: acetabular fracture
- Iliac, ischial avulsion fractures
- Displacement of the major fragment: superior (VS), open book (APC), bucket handle (LC)

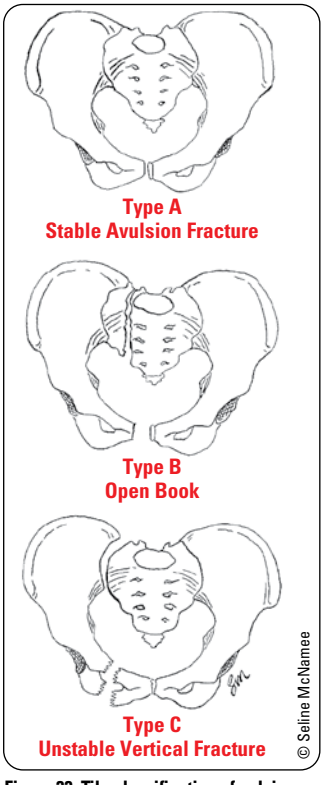



**Figure 33. Tile classification of pelvic fractures**

### Treatment
- ABCDEs
- non-operative treatment: protected weight bearing
  - indication: stable fracture (e.g. elderly patient with fracture sustained in fall from standing)
- emergency management
  - IV fluids/blood
  - pelvic binder/sheeting
  - external fixation vs. emergent angiography/embolization
  - ± laparotomy (if FAST/DPL positive)
- operative treatment: ORIF
  - indications
- unstable pelvic ring injury
- disruption of anterior and posterior SI ligament
- symphysis diastasis >2.5 cm
- vertical instability of the posterior pelvis
- open fracture

### Specific Complications (see *General Fracture Complications*, OR7)
- hemorrhage (**life-threatening**)
- injury to rectum or urogenital structures
- obstetrical difficulties, sexual and voiding dysfunction
- persistent SI joint pain
- post-traumatic arthritis of the hip with acetabular fractures
- high risk of DVT/PE

# Hip

## Hip Dislocation

- full trauma survey (see Emergency Medicine, *Patient Assessment/Management*, ER2)
- examine for neurovascular injury prior to open or closed reduction
- reduce hip dislocations within 6 h to decrease risk of AVN of the femoral head
- hip precautions (no extreme hip flexion, adduction, internal or external rotation) for 6 wk post-reduction
- see *Hip Dislocation Post-Total Hip Arthroplasty*, OR30

### ANTERIOR HIP DISLOCATION
- mechanism: posteriorly directed blow to knee with hip widely abducted
- clinical features: shortened, abducted, externally rotated limb
- treatment
  - closed reduction under conscious sedation/GA
  - post-reduction CT to assess joint congruity

### POSTERIOR HIP DISLOCATION
- most frequent type of hip dislocation
- mechanism: severe force to knee with hip flexed and adducted
  - e.g. knee into dashboard in MVC
- clinical features: shortened, adducted, internally rotated limb

Up to 50% of patients with hip dislocations suffer fractures elsewhere at the time of injury

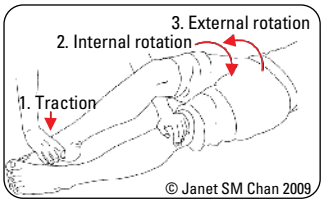



**Figure 34. Rochester method**

- treatment
  - closed reduction under conscious sedation/GA only if no associated femoral neck fracture or ipsilateral displacement
  - ORIF if unstable, intra-articular fragments, or posterior wall fracture
  - post-reduction CT to assess joint congruity and fractures
  - if reduction is unstable, put in traction x 4-6 wk

### COMPLICATIONS FOR ALL HIP DISLOCATIONS

- post-traumatic OA
- AVN of femoral head
- fracture of femoral head, neck, or shaft
- sciatic nerve palsy in 25% (10% permanent)
- HO
- thromboembolism – DVT/PE

## Hip Fracture

### General Features

- acute onset of hip pain
- unable to weight-bear
- shortened and externally-rotated leg
- painful ROM

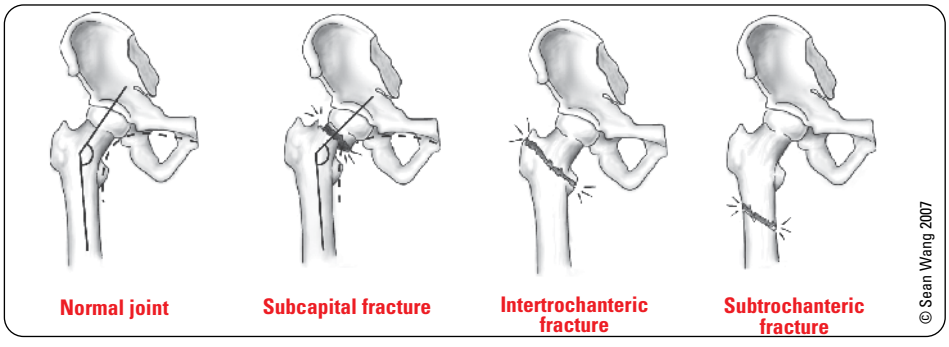



**Figure 35. Subcapital, intertrochanteric, and subtrochanteric hip fractures**

**Table 20. Overview of Hip Fractures**

| Fracture Type | Definition | Mechanism | Special Clinical Features | Investigations | Treatment | Complications |
|---|---|---|---|---|---|---|
| **Femoral Neck (Subcapital)** | Intracapsular (See *Garden Classification*, Table 21) | Young: MVC, fall from height<br>Elderly: fall from standing, rotational force | Same as general | X-Ray: AP hip, AP pelvis, cross table lateral hip | See Table 21 | DVT, non-union, AVN, dislocation |
| **Intertrochanteric**<br>Stable: intact posteromedial cortex<br>Unstable: non-intact posteromedial cortex | Extracapsular fracture including the greater and lesser trochanters and transitional bone between the neck and shaft | Same as femoral neck fracture<br>Direct or indirect force transmitted to the intertrochanteric area | Ecchymosis at back of upper thigh | X-Ray: AP pelvis, AP/lateral hip | Closed reduction under fluoroscopy then dynamic hip screw or IM nail | DVT, varus displacement of proximal fragment, malrotation, non-union, failure of fixation device |
| **Subtrochanteric** | Fracture begins at or below the lesser trochanter and involves the proximal femoral shaft | Young: high energy trauma<br>Elderly: osteopenic bone + fall, pathological fracture | Ecchymosis at back of upper thigh | X-Ray: AP pelvis, AP/lateral hip and femur | Closed/open under fluoroscopy, then plate fixation or IM nail | Malalignment, non-union, wound infection |

**X-Ray Features of Subcapital Hip Fractures**
- Disruption of Shenton's line (a radiographic line drawn along the upper margin of the obturator foramen, extending along the inferomedial side of the femoral neck)
- Altered neck-shaft angle (normal is 120-130°)

**DVT Prophylaxis in Hip Fractures**
LMWH (i.e. enoxaparin 40 mg SC bid), fondaparinux, low dose heparin on admission, do not give <12 h before surgery

**AVN of Femoral Head**
- Distal to proximal blood supply along femoral neck to head (medial and lateral femoral circumflex arteries)
- Susceptible to AVN if blood supply disrupted
- Etiology: femoral neck fracture, chronic systemic steroid use, SCFE, Legg-Calvé-Perthes, SLE, RA

**Comparative Effectiveness of Pain Management Interventions for Hip Fracture: A Systematic Review**
**Study**: Randomized controlled trials (RCTs); nonrandomized controlled trials (non-RCTs); and cohort studies of pain management techniques in older adults after acute hip fracture.
**Conclusions**: Nerve blockade seems to be effective in reducing acute pain after hip fracture. Low-level evidence suggests that preoperative traction does not reduce acute pain. Evidence was insufficient on the benefits and harms of many other interventions.

**Table 21. Garden Classification of Femoral Neck Fractures**

| Type | Displacement | Extent | Alignment | Trabeculae | Treatment |
|---|---|---|---|---|---|
| I | None | "Incomplete" | Valgus or neutral | Malaligned | Internal fixation to prevent displacement (valgus impacted fracture) |
| II | None | Complete | Neutral | Aligned | Internal fixation to prevent displacement |
| III | Some | Complete | Varus | Malaligned | Young: ORIF<br>Elderly: hemi-/total hip arthroplasty |
| IV | Complete | Complete | Varus | Aligned | Young: ORIF<br>Elderly: hemi-/total hip arthroplasty |

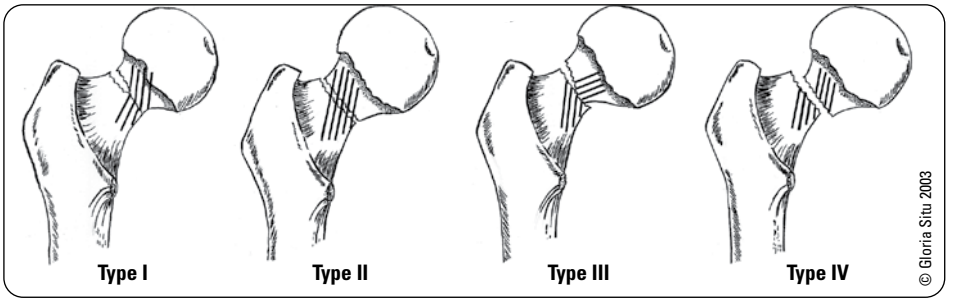



**Figure 36. Garden classification of femoral neck fractures**

# Arthritis of the Hip

### Etiology
- OA, inflammatory arthritis, post-traumatic arthritis, late effects of congenital hip disorders, or septic arthritis

### Clinical Features
- pain (groin, medial thigh) and stiffness aggravated by activity, better with rest in OA
- RA: morning stiffness >1 h, multiple joint swelling, hand nodules
- decreased ROM (internal rotation is lost first)
- crepitus
- effusion
- ± fixed flexion contracture leading to apparent limb shortening (Thomas test)
- ± Trendelenburg sign

### Investigations
- X-ray: weight-bearing views of affected joint
  - OA: joint space narrowing, subchondral sclerosis, subchondral cysts, osteophytes
  - RA: osteopenia, erosion, joint space narrowing, subchondral cysts
- blood work: ANA, RF

### Treatment
- non-operative
  - weight reduction, activity modification, physiotherapy, analgesics, walking aids
- operative
  - indication: advanced disease
  - realign = osteotomy; replace = arthroplasty; fuse = arthrodesis
- complications with arthroplasty: component loosening, dislocation, HO, thromboembolism, infection, neurovascular injury, limb length discrepancy
- arthroplasty is standard of care in most patients with hip arthritis

# Hip Dislocation Post-Total Hip Arthroplasty

- occurs in 1-4% of primary THA and 10-16% of revision THAs
- risk factors: neurological impairment, post-traumatic arthritis, revision surgery, substance abuse

### Mechanism
- THA that is unstable when hip is flexed, adducted, and internally rotated, or extended and externally rotated

### Investigations
- X-ray: AP pelvis, AP and lateral views of the hip

### Treatment
- non-operative
  - closed reduction
- operative
  - indication: 2 or more dislocations with evidence of polyethylene wear, malalignment, hardware failure
  - revision THA
  - infected hip (infection can cause hip instability)
  - conversion to hemiarthroplasty with a larger femoral head
  - resection arthroplasty is a last resort

**DVT Prophylaxis in Elective THA**
(continue 10-35 d post-operative)
DOACs (e.g. rivaroxaban), ASA, fondaparinux, low molecular weight heparin, or warfarin

### Complications
- sciatic nerve palsy in 25% (10% permanent)
- HO
- infection

# Femur

## Femoral Diaphysis Fracture

### Mechanism
- high energy trauma (MVC, fall from height, gunshot wound)
  - pathologic as a result of malignancy, osteoporosis, bisphosphonate use
- in children, can result from low energy trauma (spiral fracture)
  - always consider the possibility of non-accidental trauma

### Clinical Features
- shortened, externally rotated leg (if fracture displaced)
- inability to weight-bear
- often open injury, always a Gustilo III (Table 6)
- Winquist and Hansen classification

It is important to rule out ipsilateral femoral neck fracture, as they occur in 2-6% of femoral diaphysis fractures and are reportedly missed in 19-31% of cases

### Investigations
- X-ray: AP pelvis, AP, and lateral views of the hip, femur, knee

### Treatment
- non-operative (uncommon)
  - indication: non-displaced femoral shaft fractures in co-morbid patients
  - long leg cast
- operative
  - ORIF with anterograde IM nail (most common) or retrograde IM nail
  - external fixator for unstable patients or polytrauma with open fractures
  - early mobilization and strengthening

### Complications
- blood loss
- fat embolism leading to ARDS
- extensive soft tissue damage
- ipsilateral hip dislocation/fracture (2-6%)
- nerve injury

## Distal Femoral Fracture

- fractures from articular surface to 5 cm above metaphyseal flare

### Mechanism
- direct high energy force or axial loading
- three types: extra articular, partial articular, complete articular

### Clinical Features
- extreme pain
- knee effusion (hemarthrosis)
- neurovascular deficits can occur with displaced fracture

### Investigations
- X-ray: AP and lateral views
- CT, angiography if diminished pulses

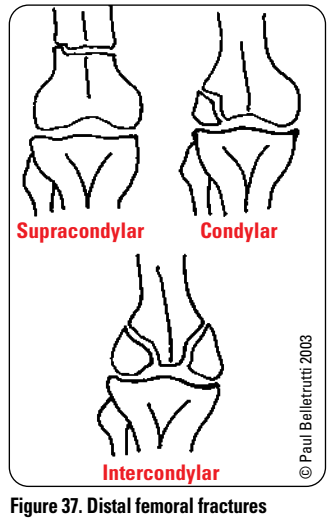



**Figure 37. Distal femoral fractures**

### Treatment
- non-operative (uncommon)
  - indication: non-displaced extra-articular fracture, poor surgical candidate
- hinged knee brace
- operative
  - indication: displaced fracture, intra-articular fracture, non-union
- ORIF or retrograde IM nail if supracondylar and non-comminuted
- early mobilization and strengthening

### Specific Complications (see *General Fracture Complications*, OR7)
- femoral artery tear
- popliteal artery injury
- nerve injury
- extensive soft tissue injury
- angulation deformities

# Knee

## Evaluation of Knee

### Common Complaints
- locking, instability, and swelling
  - torn meniscus/loose body in joint
- pseudo-locking: limited ROM without mechanical block
  - effusion, muscle spasm after injury, arthritis
- painful, audible clicking
  - torn meniscus
- giving way: instability
  - cruciate ligament or meniscal tear, patellar dislocation

### Special Tests of the Knee
- **anterior and posterior drawer tests (Figure 40)**
  - demonstrates torn ACL and PCL, respectively
  - knee flexed at 90°, foot immobilized, hamstrings released
  - if able to sublux tibia anteriorly (anterior drawer test), then ACL may be torn
  - if able to sublux tibia posteriorly (posterior drawer test), then PCL may be torn
  - anterior drawer test for ACL: 3.8 positive likelihood ratio, 0.30 negative likelihood ratio
- **Lachman test**
  - demonstrates torn ACL
  - hold knee in 10-20° flexion, stabilizing the femur
  - try to sublux tibia anteriorly on femur
  - similar to anterior drawer test, more reliable due to less muscular stabilization
  - for ACL: 25.0 positive likelihood ratio, 0.1 negative likelihood ratio
- **pivot shift sign**
  - demonstrates torn ACL
  - start with the knee in extension
  - internally rotate foot, slowly flex knee while palpating and applying a valgus force
  - if incompetent ACL, tibia will sublux anteriorly on femur at start of maneuver. During flexion, the tibia will reduce and externally rotate about the femur (the "pivot")
  - reverse pivot shift (start in flexion, externally rotate, apply valgus and extend knee) suggests torn PCL
  - composite assessment for ACL: 25.0 positive likelihood ratio, 0.04 negative likelihood ratio
  - composite assessment for PCL: 21.0 positive likelihood ratio, 0.05 negative likelihood ratio
- **posterior sag sign**
  - demonstrates torn PCL
  - may give a false positive anterior draw sign
  - flex knees and hips to 90°, hold ankles and knees
  - view from the lateral aspect
  - if one tibia sags posteriorly compared to the other, its PCL is torn
- **collateral ligament stress test**
  - palpate ligament for "opening" of joint space while testing
  - with knee in full extension, apply valgus force to test MCL, apply varus force to test LCL
  - repeat tests with knee in 20° flexion to relax joint capsule
  - opening in 20° flexion due to MCL damage only
  - opening in 20° of flexion and full extension is due to MCL, cruciate, and joint capsule damage
- **tests for meniscal tear**
  - **joint line tenderness**
    - joint line pain when palpated
    - palpate one side at a time and watch patient's eyes
    - for meniscal tear: 0.9 positive likelihood ratio, 1.1 negative likelihood ratio

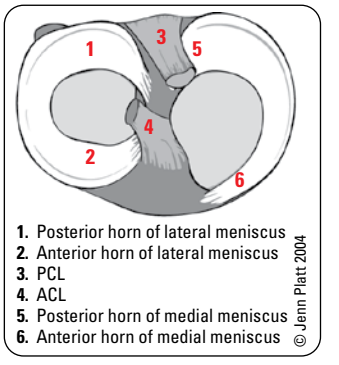



**Figure 38. Diagram of the right tibial plateau**

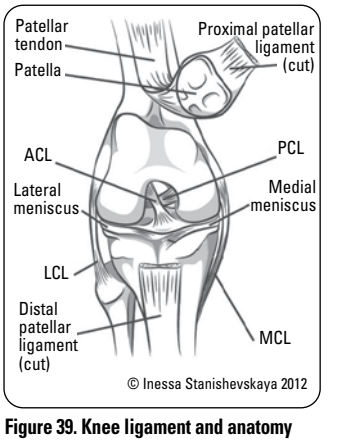



**Figure 39. Knee ligament and anatomy**

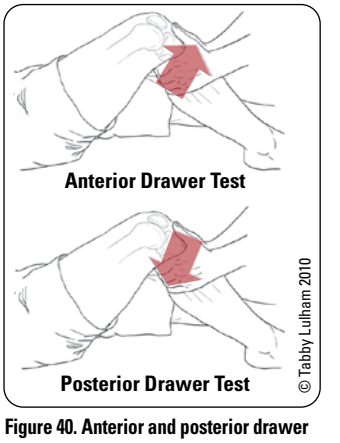



**Figure 40. Anterior and posterior drawer test**

**6 Degrees of Freedom of the Knee**
- Flexion and extension
- External and internal rotation
- Varus and valgus angulation
- Anterior and posterior glide
- Medial and lateral shift
- Compression and distraction

On physical exam of the knee, do not forget to evaluate the hip

- **crouch compression test**
  - joint line pain when squatting (anterior pain suggests patellofemoral pathology)
- **McMurray's test**
  - with knee in flexion, palpate joint line for painful pop or click
  - lateral meniscus tear exam: internally rotate foot, varus stress, and extend knee
  - medial meniscus tear exam: externally rotate foot, valgus stress, and extend knee
  - for meniscal tear: 1.3 positive likelihood ratio, 0.8 negative likelihood ratio
- **Thessaly test**
  - patient stands flat footed on one leg while the examiner provides his or her hands for balance. The patient then flexes the knee to 20° and rotates the femur on the tibia medially and laterally three times while maintaining the 20° flexion
  - positive for a meniscal tear if the patient experiences medial or lateral joint line discomfort
  - for medial meniscus: 29.67 positive likelihood ratio, 0.11 negative likelihood ratio
  - for lateral meniscus: 23.0 positive likelihood ratio, 0.083 negative likelihood ratio
  - composite assessment for meniscal tears: 2.7 positive likelihood ratio, 0.4 negative likelihood ratio

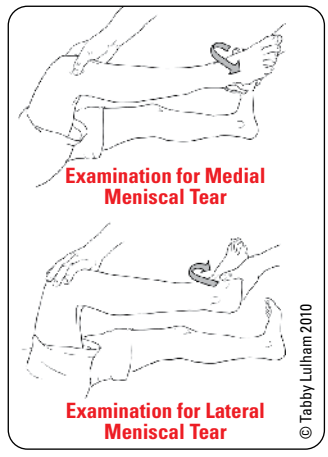


**Figure 41. McMurray test**

### X-Rays
- AP standing, lateral
- skyline: tangential view with knees flexed at 45° to see patellofemoral joint
- 3-foot standing view: useful in evaluating leg length and varus/valgus alignment
- Ottawa Knee Rules (see Emergency Medicine, ER16)

## Cruciate Ligament Tears

- ACL tear much more common than PCL tear

**Table 22. Comparison of ACL and PCL Injuries**

| | Anterior Cruciate Ligament | Posterior Cruciate Ligament |
|---|---|---|
| **Anatomy** | From medial wall of lateral femoral condyle to the anteromedial and posterolateral intercondyloid eminence of the tibial plateau | Lateral wall of medial femoral condyle to posterior intercondyloid eminence of the tibial plateau |
| **Mechanism** | Sudden deceleration<br>Hyperextension and internal rotation of tibia on femur (i.e. "plant and turn") | Sudden posterior displacement of tibia when knee is flexed or hyperextended (e.g. dashboard MVC injury) |
| **History** | Audible "pop"<br>Immediate swelling<br>Knee "giving way"<br>Inability to continue activity | Audible "pop"<br>Immediate swelling<br>Pain with push off<br>Cannot descend stairs |
| **Physical** | Effusion (hemarthrosis)<br>Posterolateral joint line tenderness<br>Positive anterior drawer<br>Positive Lachmann<br>Pivot shift<br>Test for MCL, meniscal injuries | Effusion (hemarthrosis)<br>Anteromedial joint line tenderness<br>Positive posterior drawer<br>Reverse pivot shift<br>Other ligamentous, bony injuries |
| **Treatment** | Stable knee with minimal functional impairment: immobilization 2-4 wk with early ROM and strengthening<br>High demand lifestyle: ligament reconstruction | Unstable knee or young person/high-demand lifestyle: ligament reconstruction |

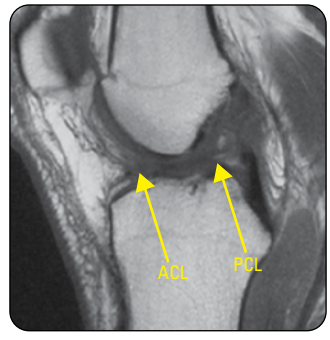


**Figure 42. T1 MRI of torn ACL and PCL**

## Collateral Ligament Tears

### Mechanism
- valgus force to knee = MCL tear
- varus force to knee = LCL tear

### Clinical Features
- swelling/effusion
- tenderness above and below joint line medially (MCL) or laterally (LCL)
- joint laxity with varus or valgus force to knee
  - laxity with endpoint suggests partial tear
  - laxity with no endpoint suggests a complete tear
- test for other injuries (e.g. O'Donoghue's unhappy triad), common peroneal nerve injury

**O'Donoghue's Unhappy Triad**
- ACL rupture
- MCL rupture
- Meniscal damage (medial and/or lateral)

### Investigations
- X-ray: AP and lateral views of the knee; MRI

### Treatment
- non-operative
  - partial tear: immobilization x 2-4 wk with early ROM and strengthening
  - complete tear: immobilization at 30° flexion
- operative
  - indication: multiple ligamentous injuries
  - surgical repair of ligaments



Partial ligamentous tears are much more painful than complete ligamentous tears

## Meniscal Tears

- medial tear much more common than lateral tear

### Mechanism
- twisting force on knee when it is partially flexed (e.g. stepping down and turning)
- requires moderate trauma in young person, but only mild trauma in elderly due to degeneration

### Clinical Features
- immediate pain, difficulty weight-bearing, instability, and clicking
- increased pain with squatting and/or twisting
- effusion (hemarthrosis) with insidious onset (24-48 h after injury)
- joint line tenderness medially or laterally
- locking of knee (if portion of meniscus mechanically obstructing extension)

### Investigations
- MRI, arthroscopy

### Treatment
- non-operative
  - indication: not locked
  - ROM and strengthening (NSAIDs)
- operative
  - indication: locked (i.e. patient cannot fully extend knee, due to mechanical block) or failed non-operative treatment
  - arthroscopic repair/partial meniscectomy



Meniscal repair is done if tear is peripheral with good vascular supply, is a longitudinal tear and 1-4 cm in length
Partial meniscectomy is done with tears not amenable to repair (complex, degenerative, radial)



**Tissue Sources for ACL Reconstruction**
- Hamstring
- Middle 1/3 patellar tendon (bone-patellar-bone)
- Allograft (e.g. cadaver)

## Popliteal Cysts

- synovial fluid-filled mass located in the popliteal fossa (i.e. Baker's cyst)

### Etiology
- classified as primary (distension of the bursa with no communication to joint) or secondary (communication between bursa and joint, bursa fills with articular fluid)
- primary cysts are usually congenital in children, while secondary are acquired from traumatic injury or degenerative/inflammatory joint disease in adults

### Clinical Features
- usually asymptomatic bulge on the posterior aspect of the knee
- usually located between the semimembranosus and medial head of gastrocnemius
- may cause local tightness, restricted range of motion or posterior knee pain
- symptoms may worsen with physical activity
- for secondary popliteal cysts, symptoms are more associated with the underlying condition of the knee

### Investigations
- clinical diagnosis is often sufficient
- ultrasonography can be used to identify cyst and its relation to adjacent soft tissue structures
- knee X-ray to assess for joint abnormalities that may be associated with the cyst
- MRI allows for clearest visualization but this is only indicated to plan for surgery, when an underlying knee pathology such as a meniscal tear is suspected, or when the diagnosis is uncertain after ultrasonography

### Treatment
- asymptomatic cysts do not require treatment
- non-operative
  - indication: initial treatment for symptomatic secondary popliteal cysts
  - identify and treat underlying cause
  - rest, NSAIDs, cold packs for symptomatic treatment
  - aspiration and intra-articular steroid injection may offer temporary relief
- operative
  - indication: primary symptomatic popliteal cyst, resistant to initial treatment, absence of identifiable joint pathology
  - surgical excision using a posterior approach

# Quadriceps/Patellar Tendon Rupture

### Mechanism
- sudden forceful contraction of quadriceps during an attempt to stop
- more common in obese patients and those with pre-existing degenerative changes in tendon
  - DM, SLE, RA, steroid use, renal failure on dialysis

### Clinical Features
- inability to extend knee or weight-bear
- possible audible "pop"
- patella in lower or higher position with palpable gap above or below patella, respectively
- may have an effusion

Patella alta = high riding patella
Patella baja (infera) = low riding patella

### Investigations
- ask patient to perform straight leg raise (unable to with complete rupture)
- knee X-ray to rule out patellar fracture, MRI to distinguish between complete and partial tears
- lateral view: patella alta with patella tendon rupture, patella baja (infera) with quadriceps tendon rupture

### Treatment
- non-operative
  - indication: incomplete tears with preserved extension of knee
  - immobilization in brace
- operative
  - indication: complete ruptures with loss of extensor mechanism
- early surgical repair: better outcomes compared with delayed repair (>6 wk post-injury)
- delayed repair complicated by quadriceps contracture, patella migration, and adhesions

# Dislocated Knee

### Mechanism
- high energy trauma
- by definition, caused by tears of multiple ligaments

### Clinical Features
- classified by relation of tibia with respect to femur
  - anterior, posterior, lateral, medial, rotary
- knee instability
- effusion
- pain
- ischemic limb
- Schenck classification

**Schenck Classification**
Type 1: Single ligament injury (ACL or PCL)
Type 2: Injury to ACL and PCL
Type 3: Injury to ACL, PCL and either MCL or LCL
Type 4: Injury to ACL, PCL, MCL, LCL
Type 5: Multiligamentous injury with periarticular fracture

### Investigations
- X-ray: AP, lateral, and skyline views of the knee
  - associated radiographic findings include tibial plateau fracture dislocations, proximal fibular fractures, and avulsion of fibular head
- Assessment of NVS:
  - ABI (abnormal if <0.9)
  - arteriogram or CT angiogram if abnormal vascular exam (such as abnormal pedal pulses)
  - assessment of peroneal nerve, tibial artery, and ligamentous injuries

### Treatment
- urgent closed reduction
  - complicated by interposed soft tissue
- assessment of peroneal nerve, tibial artery, and ligamentous injuries
- emergent operative repair if vascular injury, open fracture or dislocation, irreducible dislocation, compartment syndrome
- knee immobilization x 6-8 wk

### Specific Complications
- high incidence of associated injuries
- popliteal artery tear
- peroneal nerve injury
- capsular tear
- chronic: instability, stiffness, post-traumatic arthritis

# Patella

## Patellar Fracture

### Mechanism
- direct blow to the patella: fall, MVC (dashboard)
- indirect trauma by sudden flexion of knee against contracted quadriceps

### Clinical Features
- marked tenderness
- inability to extend knee or straight leg raise
- proximal displacement of patella
- patellar deformity
- ± effusion/hemarthrosis

### Investigations
- X-rays: AP, lateral, skyline
- do not confuse with bipartite patella: congenitally unfused ossification centres with smooth margins on X-ray at superolateral corner

### Treatment
- non-operative
  - indication: non-displaced (step-off <2-3 mm and fracture gap <1-4 mm)
- straight leg immobilization 1-4 wk with hinged knee brace, weight bearing as tolerated
- progress in flexion after 2-3 wk
- physiotherapy: quadriceps strengthening when pain has subsided
- operative
  - indication: displaced (>2 mm), comminuted, disrupted extensor mechanism
  - ORIF, if comminuted may require partial/complete patellectomy
- goal: restore extensor mechanism with maximal articular congruency

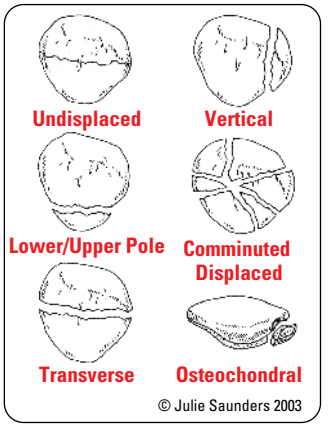



**Figure 43. Types of patellar fractures**

**Complications**
- Symptomatic wiring
- Loss of reduction
- Osteonecrosis (proximal fragment)
- Hardware failure
- Knee stiffness
- Nonunion
- Infection

## Patellar Dislocation

### Mechanism
- usually a non-contact twisting injury
- lateral displacement of patella after contraction of quadriceps at the start of knee flexion in an almost straight knee joint
- direct blow e.g. knee/helmet to knee collision

### Risk Factors
- young, female
- obesity
- high-riding patella (patella alta)
- genu valgus
- Q-angle (quadriceps angle) ≥20°
- shallow intercondylar groove
- weak vastus medialis
- tight lateral retinaculum
- ligamentous laxity (Ehlers-Danlos)

### Clinical Features
- knee catches or gives way with walking
- severe pain, tenderness anteromedially from rupture of capsule
- weak knee extension or inability to extend leg unless patella reduced
- positive patellar apprehension test
  - passive lateral translation results in guarding and patient apprehension
- often recurrent, self-reducing
- concomitant MCL injury
- increased Q-angle
- J-sign

### Investigations
- X-rays: AP, lateral, and skyline views of the knee
- check for fracture of medial patella (most common) and lateral femoral condyle

### Treatment
- non-operative first
  - NSAIDs, activity modification, and physical therapy
  - short-term immobilization for comfort, then 6 wk controlled motion
  - progressive weight bearing and isometric quadriceps strengthening
- operative
  - indication: if recurrent or if loose bodies present
  - surgical tightening of medial capsule and release of lateral retinaculum, possible tibial tuberosity transfer, or proximal tibial osteotomy

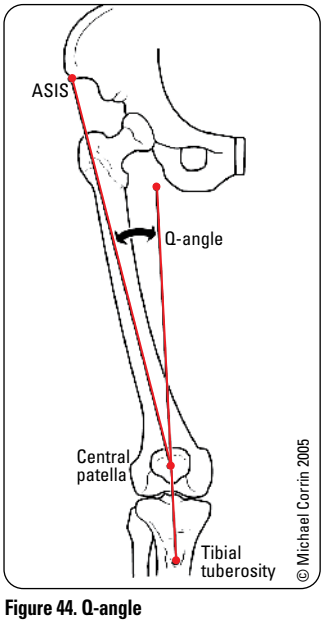



**Figure 44. Q-angle**
The angle between a vertical line through the patella and tibial tuberosity and a line from the ASIS to the middle patella; the larger the angle, the greater the amount of lateral force on the knee (normal <20°)

**J-sign:** Associated with patella alta; increased lateral translation in extension which pops into the patellofemoal groove as the patella engages the trochlea early in flexion

## Patellofemoral Syndrome (Chondromalacia Patellae)

- syndrome of anterior knee pain associated with idiopathic articular changes of patella

### Risk Factors
- malalignment causing patellar maltracking (Q angle ≥20°, genu valgus)
- post-trauma
- deformity of patella or femoral groove
- recurrent patellar dislocation, ligamentous laxity
- excessive knee strain (athletes)

### Mechanism
- softening, erosion, and fragmentation of articular cartilage, predominantly medial aspect of patella
- commonly seen in active young females

### Clinical Features
- deep, aching anterior knee pain
  - exacerbated by prolonged sitting (theatre sign), strenuous athletic activities, stair climbing, squatting, or kneeling
- insidious onset and vague in nature
- sensation of instability, pseudolocking
- pain with extension against resistance through terminal 30-40°
- pain with compression of patella with knee ROM or resisted knee extension
- swelling rare, minimal if present
- palpable crepitus



Pain with firm compression of patella into medial femoral groove is pathognomonic of patellofemoral syndrome

### Investigations
- X-ray: AP, lateral, and skyline views of the knee – may find chondrosis, lateral patellar tilt, patella alta/baja, or shallow sulcus
- CT-scan
- MRI – best to assess articular cartilage

### Treatment
- non-operative
  - continue non-impact activities; rest and rehabilitation
  - NSAIDs
  - physiotherapy: vastus medialis and core strengthening
- operative
  - indication: failed non-operative treatment
  - tibial tubercle elevation
  - arthroscopic shaving/debridement
  - lateral release of retinaculum

# Tibia

## Tibial Plateau Fracture

### Mechanism
- varus/valgus load ± axial loading (e.g. fall from height)
- femoral condyles driven into proximal tibia
- can result from minor trauma in those with osteoporosis

### Clinical Features
- frequency: lateral > bicondylar > medial
- medial fractures require higher energy – often have concomitant vascular injuries
- knee effusion
- inability to bear weight
- swelling
- risk of compartment syndrome, ACL injury, meniscal tears and vascular injuries
- Schatzker classification



**Schatzker Classification**

| Type | Description |
|---|---|
| I | Involvement of lateral plateau split fracture |
| II | Lateral split-depressed fracture |
| III | Involvement of lateral plateau: pure depression fracture |
| IV | Medial plateau fracture |
| V | Bicondylar plateau fracture |
| VI | Bicondylar with metaphyseal/diaphyseal involvement |

### Investigations
- X-ray: AP, lateral, and oblique views
- CT: pre-operative planning, identify articular depression and comminution
- ABI if any differences in pulses between extremities

### Treatment

| | |
|---|---|
| **Approach #1 (based on amount of depression seen on x-ray)** | **Non-operative indication** (if depression on x-ray is <3 mm): hinged knee brace, PWB 8-12 wk, immediate passive ROM<br>**Operative indication** (if depression is >3 mm, all medial plateau or bicondylar fractures): ORIF often requiring bone grafting to elevate depressed fragment |
| **Approach #2 (based on varus/valgus instability)** | **Non-operative indication** (if minimal varus/valgus instability [<15°]): straight leg immobilization x 4-6 wk with progressive ROM weight bearing<br>**Operative indication** (if significant varus/valgus instability [>15°]): ORIF often requiring bone grafting to elevate depressed fragment |

### Specific Complications (see *General Fracture Complications*, OR7)
- ligamentous injuries
- meniscal lesions
- AVN
- infection
- OA

## Tibial Shaft Fracture

- most common long bone fracture and open fracture

### Mechanism
- low energy pattern: torsional injury
- high energy: including MVC, falls, sporting injuries

### Clinical Features
- pain, inability to weight bear
- open vs. closed
- neurovascular compromise

### Investigations
- X-ray: AP and lateral views
  - full length, plus knee and ankle

### Treatment
- non-operative
  - indication: closed and minimally displaced or adequate closed reduction
- long leg cast x 8-12 wk, functional brace after
- operative
  - indication: displaced or open
- if displaced and closed: ORIF with IM nail, plate and screws, or external fixator
- if open: antibiotics, I&D, external fixation or IM nail, and vascularized coverage of soft tissue defects

### Specific Complications (see *General Fracture Complications*, OR7)
- high incidence of neurovascular injury and compartment syndrome
- poor soft tissue coverage (critical to outcome)



**Figure 45. Tibial shaft fracture treated with IM nail and screws**

Tibial shaft fractures have high incidence of compartment syndrome and are often associated with soft tissue injuries

**Danis-Weber Classification**
- Based on level of fibular fracture relative to syndesmosis

**Type A (infra-syndesmotic)**
- Pure inversion injury, tibiofibular syndesmosis remains intact
- Avulsion of lateral malleolus below plafond or torn calcaneofibular ligament
- ± shear fracture of medial malleolus

**Type B (trans-syndesmotic)**
- External rotation and eversion (most common)
- ± avulsion of medial malleolus or rupture of deltoid ligament
- Spiral fracture of lateral malleolus starting at plafond

**Type C (supra-syndesmotic)**
- Pure external rotation
- Avulsion of medial malleolus or torn deltoid ligament
- ± posterior malleolus avulsion with posterior tibio-fibular ligament
- Fibular fracture is above plafond
- frequently tears syndesmosis

**Ottawa Ankle Rules** (see Emergency Medicine, ER17)

X-rays are only required if:

Pain in the malleolar zone AND bony tenderness over the distal 6 cm of the posterior aspect of the tibia or tip of the medial or lateral malleolus OR inability to weight bear both immediately after injury and in the ER

# Ankle

## Evaluation of Ankle and Foot Complaints

### Special Tests
- anterior drawer: examiner attempts to displace the foot anteriorly against a fixed tibia
- talar tilt: foot is stressed in inversion and angle of talar rotation is evaluated by X-ray

### X-Ray
- AP and lateral views
- mortise view: ankle at 15° of internal rotation
  - gives true view of ankle joint
  - joint space should be symmetric with no talar tilt
- Ottawa Ankle Rules should guide X-ray use (see Emergency Medicine, ER17); nearly 100% sensitivity
- ± CT to better characterize fractures

# Ankle Fracture

### Mechanism
- pattern of fracture depends on the position of the ankle when trauma occurs
- generally involves
  - ipsilateral ligamentous tears or transverse bony avulsion
  - contralateral shear fractures (oblique or spiral)
- classification systems
  - Danis-Weber
  - Lauge-Hansen: based on foot's position and motion relative to leg

### Treatment
- non-operative
  - indication: non-displaced, no history of dislocation
  - below knee cast, NWB, or aircast WBAT
- operative
  - indications
    - any fracture-dislocation: restore vascularity, minimize articular injury, reduce pain and skin pressure
    - most of type B, and all of type C
    - trimalleolar (medial, posterior, lateral) fractures
    - talar tilt >10°
    - medial clear space on X-ray greater than superior clear space
    - open fracture/open joint injury
  - ORIF

### Complications
- high incidence of post-traumatic arthritis
- high risk of poor wound healing and deep infections (up to 20%) for patients with DM

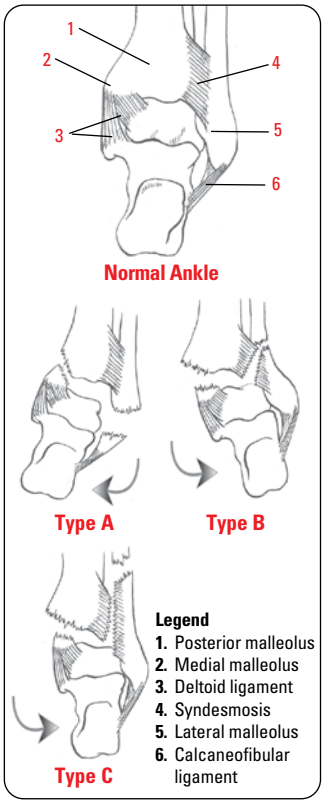



**Figure 46. Ring principle of the ankle and Danis-Weber classification**

# Ankle Ligamentous Injuries

- see Figure 47 for ankle ligaments

### Medial Ligament Complex (deltoid ligament)
- eversion injury
- usually avulses medial or posterior malleolus and strains syndesmosis

### Lateral Ligament Complex (anterior talofibular, calcaneofibular, posterior talofibular)
- inversion injury, >90% of all ankle sprains
- ATF most commonly and severely injured if ankle is plantarflexed
- swelling and tenderness anterior to lateral malleolus
- ++ ecchymosis
- positive ankle anterior drawer
- may have significant medial talar tilt on inversion stress X-ray

### Treatment
- non-operative
  - microscopic tear (Grade I)
    - rest, ice, compression, elevation
  - macroscopic tear (Grade II)
    - strap ankle in dorsiflexion and eversion x 4-6 wk
    - physiotherapy: strengthening and proprioceptive retraining
  - complete tear (Grade III)
    - below knee walking cast x 4-6 wk
    - physiotherapy: strengthening and proprioceptive retraining
    - surgical intervention may be required if chronic symptomatic instability develops

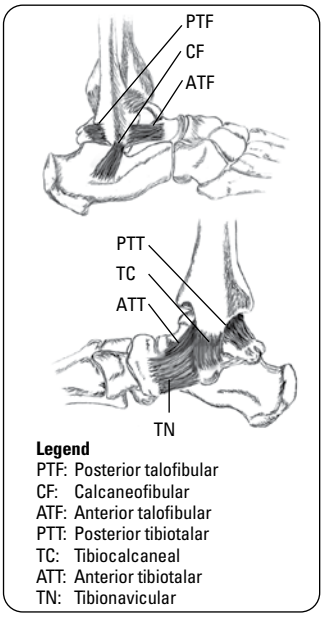



**Figure 47. Ankle ligament complexes**

With a history of significant trauma from axial loading of lower limb, always consider spinal injuries, femoral neck, tibial plateau, and talar/calcaneal fractures

# Foot

## Talar Fracture

### Mechanism
- axial loading or hyperdorsiflexion commonly from MVC or fall from height
- 60% of talus covered by articular cartilage
- talar neck is most common fracture of talus (50%)
- tenuous blood supply runs distal to proximal along talar neck
  - high risk of AVN with displaced fractures

### Investigations
- X-ray: AP, lateral, and Canale views (maximum equinus, 15 degrees pronated) of the foot
- CT to better characterize fracture
- MRI can clearly define extent of AVN

### Treatment
- non-operative
  - indication: non-displaced
  - NWB, below-knee cast x 6 wk
- operative
  - indication: displaced
  - ORIF (high rate of nonunion, AVN)
  - neck fracture: ORIF

## Calcaneal Fracture

- most common tarsal fracture

### Mechanism
- high energy, axial loading: fall from height onto heels
- 10% of fractures associated with compression fractures of thoracic or lumbar spine (rule out spine injury)
- 75% are intra-articular and 10% are bilateral

**Calcaneal Fracture Treatment Principles**
- Avoid wound complications (10-25%)
- Restore articular congruity
- Restore normal calcaneal width and height
- Maximum functional recovery may take longer than 12 mo

### Clinical Features
- marked swelling, bruising on heel/sole
- wider, shortened, flatter heel when viewed from behind
- varus heel

### Investigations
- X-rays: AP, lateral, and oblique foot (mandatory views); can also assess with Broden view, Harris view, or AP ankle
- loss of Bohler's angle
- CT: gold-standard, assess intra-articular extension

### Treatment
- closed vs. open reduction is controversial
- NWB cast x 3 mo with early ROM and strengthening

## Achilles Tendonitis

### Mechanism
- chronic inflammation from activity or poor-fitting footwear
- may also develop heel bumps (i.e. retrocalcaneobursitis or Haglund deformity)

**Haglund Deformity**: an enlargement of the posterior-superior tuberosity of the calcaneus

### Clinical Features
- pain, stiffness, and crepitus with ROM
- thickened tendon, palpable bump

### Investigations
- X-ray: lateral, evaluate bone spur and calcification; U/S, MRI (to assess degenerative change)

### Treatment
- non-operative
  - rest, NSAIDs, shoe wear modification (orthotics, open back shoes)
  - heel sleeves and pads are mainstay of non-operative treatment
  - gentle gastrocnemius-soleus stretching, eccentric training with physical therapy, deep tissue calf massage
  - shockwave therapy in chronic tendonitis
  - do not inject steroids (risk of tendon rupture)

# Achilles Tendon Rupture

### Mechanism
- loading activity, stop-and-go sports (e.g. squash, tennis, basketball)
- secondary to chronic tendonitis, steroid injection

### Clinical Features
- audible pop, sudden pain with push-off movement
- pain or inability to plantarflex
- palpable gap
- apprehensive toe off when walking
- weak plantarflexion strength
- Thompson test: with patient prone, squeeze calf, normal response is plantar flexion
  - no passive plantarflexion is positive test = ruptured tendon

### Investigations
- X-ray (to rule out other pathology), U/S or MRI (for partial vs. complete ruptures)

### Treatment
- non-operative
  - indication: low athletic demand (new level 1 evidence suggests no difference in re-rupture rates between operative and non-operative management with functional rehabilitation)
  - initial cast foot in plantar flexion (to relax tendon), with functional rehabilitation x 8-12 wk
- operative
  - indication: high athletic demand
  - surgical repair, followed by functional rehabilitation x 8-12 wk

The most common site of Achilles tendon rupture is 2-6 cm from its insertion where the blood supply is the poorest

**Complications of Achilles Tendon Rupture**
- Infection
- Sural nerve injury
- Re-rupture: surgical repair decreases likelihood of re-rupture compared to non-operative management

# Plantar Fasciitis (Heel Spur Syndrome)

### Definition
- inflammation of plantar aponeurosis at calcaneal origin
- common in athletes (especially runners, dancers)
- also associated with obesity, DM, seronegative and seropositive arthritis

### Mechanism
- repetitive strain injury causing microtears and inflammation of plantar fascia

### Clinical Features
- insidious onset of heel pain, pain when getting out of bed, and stiffness
- intense pain when walking from rest that subsides as patient continues to walk, worse at end of day with prolonged standing
- swelling, tenderness over sole
- greatest at medial calcaneal tubercle and 1-2 cm distal along plantar fascia
- pain with toe dorsiflexion (stretches fascia)

### Investigations
- plain radiographs to rule out fractures
- often see bony exostoses (heel spurs) at insertion of fascia into medial calcaneal tubercle
- spur is secondary to inflammation, not the cause of pain

### Treatment
- non-operative
  - pain control and stretching programs are first-line
  - rest, ice, NSAIDs, steroid injection
  - physiotherapy: Achilles tendon and plantar fascia stretching, extracorporeal shockwave therapy
  - orthotics with heel cup – to counteract pronation and disperse heel strike forces
- operative
  - very rarely indicated
  - when performed, includes endoscopic release of fascia

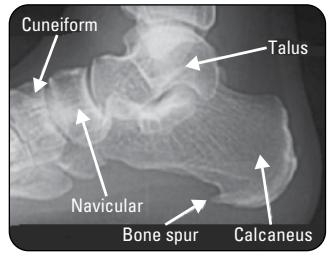


**Figure 48. X-ray of bony heel spur**

**Surgical vs. Nonsurgical Methods for Acute Achilles Tendon Rupture: A Meta-Analysis of Randomized Controlled Trials**
J Foot Ankle Surg Am. 2018 Nov - Dec; 57(6): 1191-1199
**Purpose**: To compare surgical treatment and conservative treatment of acute Achilles tendon rupture.
**Methods**: A meta-analysis was performed looking at randomized trials comparing surgical with nonsurgical treatment or comparing different surgical treatments of Achilles tendon rupture.
**Results**: 10 randomized clinical trials with a total of 934 randomized patients were included. Patients in the non-surgical group had a higher re-rupture rate than patients in the surgical group. However, re-rupture rates were equivalent (p = .08) if an early range of motion exercises protocol was performed. Lower incidence of complications (excluding re-rupture) was found in non-surgical patients.
**Conclusions**: Non-surgical treatment for acute Achilles tendon rupture is preferred if a functional rehabilitation protocol with early range of motion is possible. If not, surgical treatment should be considered because of the lower rate of re-rupture.

# Bunions (Hallux Valgus)

### Definition
- bony deformity characterized by medial displacement of first metatarsal and lateral deviation of hallux

### Mechanism
- many associated deformities in foot from altered mechanics
- valgus alignment of 1st MTP (hallux valgus), loose medial and tight lateral joint capsule, adductor hallucis becomes a deforming force
- formation of a reactive exostosis and thickening of the skin creates a bunion
- associated with poor-fitting footwear (high heel and narrow toe box)
- can be hereditary (70% have family history)
- 10x more frequent in women

### Clinical Features
- painful bursa over medial eminence of 1st MT head
- pronation (rotation inward) of great toe
- numbness over medial aspect of great toe

### Investigations
- X-ray: standing AP/lateral/sesamoid view, NWB oblique

### Treatment
- indications: painful corn or bunion, overriding 2nd toe
- non-operative (first-line)
  - properly fitted shoes (low heel) and toe spacer
- operative: goal is to restore normal anatomy, not cosmetic reasons alone
  - osteotomy with realignment of 1st MTP joint (Chevron Procedure)
  - arthrodesis

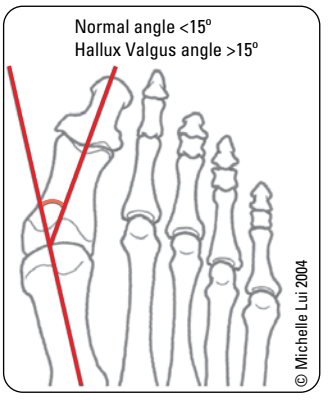



**Figure 49. Hallux valgus**

## Metatarsal Fracture

- as with the hand, 1st, 4th, 5th MT are relatively mobile, while the 2nd and 3rd are fixed
- use Ottawa Foot Rules to determine need for x-ray

**Table 23. Types of Metatarsal Fractures**

| Fracture Type | Mechanism | Clinical | Treatment |
|---|---|---|---|
| **Avulsion of Base of 5th MT** | Sudden inversion followed by contraction of peroneus brevis | Tender base of 5th MT | Conservative management |
| **Proximal Shaft of 5th MT (Jones Facture)** | Stress injury | Painful over base of 5th MT | *NWB BK cast x 6 wk<br>ORIF if athlete |
| **Shaft 2nd, 3rd MT (March Fracture)** | Stress injury | Painful shaft of 2nd or 3rd MT | Symptomatic |
| **1st MT** | Trauma | Painful 1st MT | ORIF if displaced otherwise<br>*NWB BK cast x 3 wk then walking cast x 2 wk |
| **Tarso-MT Fracture – Dislocation (Lisfranc Fracture)** | Fall onto plantar flexed foot or direct crush injury | Pain over base of 2nd MT<br>Swelling over midfoot<br>Inability to bear weight | ORIF |

*NWB BK = Non weight bearing, below knee

**Ottawa Ankle and Foot Rules**
(see Emergency Medicine, ER17)
X-rays only required if:
Pain in the midfoot zone AND bony tenderness over the navicular or base of the fifth metatarsal OR inability to weight bear both immediately after injury and in the ER

# Pediatric Orthopedics

## Fractures in Children

- type of fracture
  - thicker, more active periosteum results in pediatric-specific fractures: greenstick (one cortex), torus (i.e. 'buckle', impacted cortex) and plastic (bowing)
  - distal radius fracture most common in children (phalanges second), the majority are treated with closed reduction and casting
  - adults fracture through both cortices
- epiphyseal growth plate
  - weaker part of bone, susceptible to fractures
  - plate often mistaken for fracture on x-ray and vice versa (X-ray opposite limb for comparison), especially in elbow
  - tensile strength of bone < ligaments in children, therefore clinician must be confident that fracture and/or growth plate injury have been ruled out before diagnosing a sprain
  - intra-articular fractures have worse consequences in children because they usually involve the growth plate
- anatomic reduction
  - gold standard with adults
  - accept greater angular deformity in children (remodelling minimizes deformity)
- time to heal
  - shorter in children
- always be aware of the possibility of child abuse
  - make sure stated mechanism compatible with injury
  - high index of suspicion with fractures in non-ambulating children (<1 yr); look for other signs, including X-ray evidence of healing fractures at different sites and different stages of healing
  - common suspicious fractures in children: metaphyseal corner fracture (hallmark of non-accidental trauma), femur fracture <1 year old, humeral shaft <3 year old, sternal fractures, posterior rib fractures, spinous process fractures

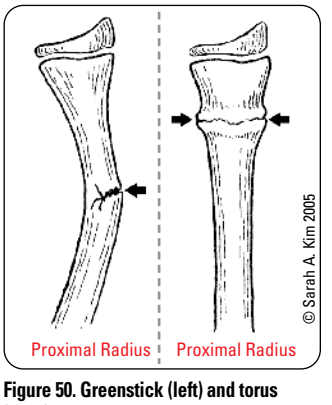



**Figure 50. Greenstick (left) and torus (right) fractures**

Greenstick fractures are easy to reduce but can redisplace while in cast due to intact periosteum

# Stress Fractures

### Mechanism
- insufficiency fracture
  - stress applied to a weak or structurally deficient bone
- fatigue fracture
  - repetitive, excessive force applied to normal bone
- most common in adolescent athletes
- common in tibia, calcaneus, and metatarsals

### Diagnosis
- localized pain and tenderness over the involved bone
- plain films may not show fracture for 2 wk
- bone scan positive in 12-15 d

### Treatment
- rest from strenuous activities to allow remodelling (can take several months)

# Physeal Injury

**Table 24. Salter-Harris Classification of Epiphyseal Injury**

| SALT(E)R–Harris Type | Description | Treatment |
|---|---|---|
| **I (Straight through; Stable)** | Transverse through growth plate | Closed reduction and cast immobilization (except SCFE – ORIF); heals well, 95% do not affect growth |
| **II (Above)** | Through metaphysis and along growth plate | Closed reduction and cast if anatomic; otherwise ORIF |
| **III (Low)*** | Through epiphysis to plate and along growth plate | Anatomic reduction by ORIF to prevent growth arrest, avoid fixation across growth plate |
| **IV (Through and through)*** | Through epiphysis and metaphysis | Closed reduction and cast if anatomic; otherwise ORIF |
| **V (Ram)*** | Crush injury of growth plate | High incidence of growth arrest; no specific treatment |

* Types III – IV are more likely to cause growth arrest and progressive deformity

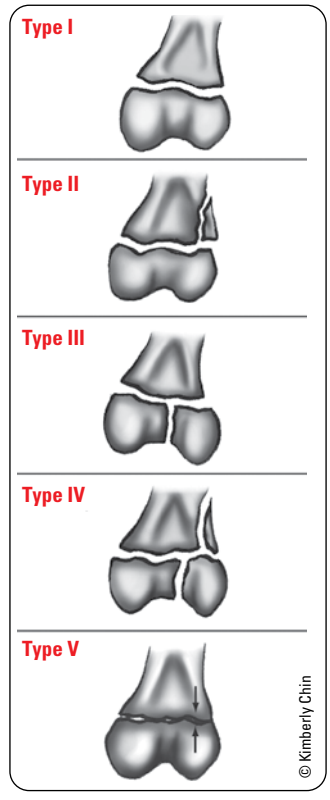



**Figure 51. Salter-Harris classification**

# Slipped Capital Femoral Epiphysis

- most common adolescent hip disorder, peak incidence at pubertal growth spurt

### Definition
- type I Salter-Harris epiphyseal injury at proximal hip

### Etiology
- multifactorial
  - genetic: autosomal dominant, black children at highest risk
  - cartilaginous physis hypertrophies too rapidly under growth hormone effects
  - sex hormone secretion, which stabilizes physis, has not yet begun
  - overweight: mechanical stress
  - trauma: causes acute slip
- risk factors: male, obese (#1 factor), hypothyroid (risk of bilateral involvement)

### Clinical Features
- acute: sudden, severe pain with limp
- chronic: typically groin and anterior thigh pain, may present with knee pain
  - positive Trendelenburg sign on affected side, due to weakened gluteal muscles
- tender over joint capsule
- restricted internal rotation, abduction, flexion
  - Whitman's sign: obligatory external rotation during passive flexion of hip
- Loder classification: stable vs. unstable (provides prognostic information)
  - unstable means patient cannot ambulate even with crutches

Bilateral involvement occurs in about 25%

### Investigations
- X-ray: AP, frog-leg, lateral radiographs both hips
  - posterior and medial slip of epiphysis
  - disruption of Klein's line
  - AP view may be normal or show widened/lucent growth plate compared with opposite side

**Klein's Line**
On AP view, line drawn along supero-lateral border of femoral neck should cross at least a portion of the femoral epiphysis. If it does not, suspect SCFE

### Treatment
- operative
  - mild/moderate slip: stabilize physis with pins in current position
  - severe slip: ORIF or pin physis without reduction and osteotomy after epiphyseal fusion

### Complications
- AVN (roughly half of unstable SCFEs), chondrolysis (loss of articular cartilage, resulting in narrowing of joint space), pin penetration, premature OA, loss of ROM

## Developmental Dysplasia of the Hip

### Definition
- abnormal development of hip, resulting in dysplasia and subluxation/dislocation of hip
- most common orthopedic disorder in newborns

### Etiology
- due to ligamentous laxity, muscular underdevelopment, and abnormal shallow slope of acetabular roof
- spectrum of conditions
  - dislocated femoral head completely out of acetabulum
  - dislocatable head in socket
  - head subluxates out of joint when provoked
  - dysplastic acetabulum, more shallow and more vertical than normal

### Physical Exam
- diagnosis is clinical
  - limited abduction of the flexed hip (<60°)
  - affected leg shortening results in asymmetry in skin folds and gluteal muscles, wide perineum
  - Barlow's test checks if hips are dislocatable
    - flex hips and knees to 90° and grasp thigh
    - fully adduct hips, push posteriorly to try to dislocate hips
  - Ortolani's test checks if hips are dislocated
    - initial position as above but try to reduce hip with fingertips during abduction
    - positive test: palpable clunk is felt (not heard) if hip is reduced
  - Galeazzi's sign
    - knees at unequal heights when hips and knees flexed
    - dislocated hip on side of lower knee
    - difficult test if child <1 yr
    - Trendelenburg test and gait useful if older (>2 yr)

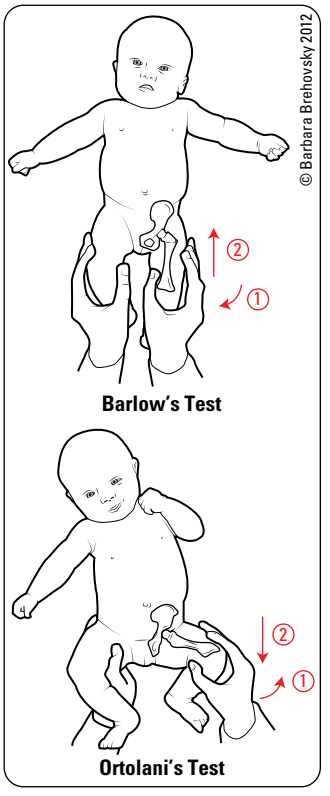



**Figure 52. Barlow's test and Ortolani's test**

### Investigations
- U/S in first few months to view cartilage (bone is not calcified in newborns until 4-6 mo)
- follow-up radiograph after 3 mo
- X-ray signs (at 4-6 mo): false acetabulum, acetabular index >25°, broken Shenton's line, femoral neck above Hilgenreiner's line, ossification centre outside of inner lower quadrant (quadrants formed by intersection of Hilgenreiner's and Perkin's lines) (Figure 56)

### Treatment
- 0-6 mo: reduce hip using Pavlik harness to maintain abduction and flexion
- 6-18 mo: reduction under GA, hip spica cast x 2-3 mo (if Pavlik harness fails)
- >18 mo: open reduction; pelvic and/or femoral osteotomy

### Complications
- redislocation, inadequate reduction, stiffness
- AVN of femoral head

**5 Fs that Predispose to Developmental Dysplasia of the Hip**
**F**amily history
**F**emale
**F**rank breech
**F**irst born
Le**F**t hip

## Legg-Calvé-Perthes Disease (Coxa Plana)

### Definition
- idiopathic AVN of femoral head, presents at 4-8 yr of age
- 12% bilateral, M>F = 5:1, 1/1200
- associations
  - family history
  - low birth weight
  - abnormal pregnancy/delivery
  - ADHD in 33% of cases, delayed bone age in 89%
  - second-hand smoke exposure
  - Asian, Inuit, Central European
- key features
  - AVN of proximal femoral epiphysis, abnormal growth of the physis, and eventual remodelling of regenerated bone

Most common in adolescent athletes, especially jumping/sprinting sports

Children diagnosed with coxa plana <6 yr of age have improved prognosis

### Clinical Features
- child with antalgic or Trendelenburg gait ± pain
- intermittent knee, hip, groin, or thigh pain
- flexion contracture (stiff hip): decreased internal rotation and abduction of hip
- limb length discrepancy (late)

### Investigations
- X-ray: AP pelvis, frog leg laterals
- initially, may be negative; if high index of suspicion, move to bone scan or MRI
- eventually, collapse of femoral head will be seen (diagnostic)

### Treatment
- goal is to preserve ROM and keep femoral head contained in acetabulum
- non-operative
  - physiotherapy: ROM exercises
  - brace in flexion and abduction x 2-3 yr (controversial)
- operative
  - femoral or pelvic osteotomy (>8 yr of age or severe)
    - prognosis better in males, <6 yr, <50% of femoral head involved, abduction >30°
- 60% of involved hips do not require operative intervention
- natural history is early onset OA and decreased ROM

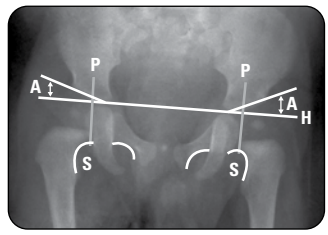



**Figure 53. Pelvic x-ray and reference lines and angles for assessment of DDH**
**Triradiate Cartilage**
y-shaped epiphyseal plate at junction of ilium, ischium and pubis
**Hilgenreiner's Line**
Line running between triradiate cartilages
**Perkin's Line**
Line through lateral margin of acetabulum, perpendicular to Hilgenreiner's Line
**Shenton's Line**
Arced line along inferior border of femoral neck and superior margin of obturator foramen
**Acetabular Index**
Angle between Hilgenreiner's Line and line from triradiate cartilage to point on lateral margin of acetabulum

## Osgood-Schlatter Disease

### Definition
- inflammation of patellar ligament at insertion point on tibial tuberosity
- M>F; boys 12-15 yr; girls 8-12 yr

### Mechanism
- repetitive tensile stress on insertion of patellar tendon over the tibial tuberosity causes minor avulsion at the site and subsequent inflammatory reaction (tibial tubercle apophysitis)

### Clinical Features
- tender lump over tibial tuberosity
- pain on resisted leg extension
- anterior knee pain exacerbated by jumping or kneeling, relieved by rest

### Investigations
- X-ray lateral knee: fragmentation of the tibial tubercle, ± ossicles in patellar tendon

### Treatment
- benign, self-limited condition, does not resolve until growth halts
- non-operative (majority)
  - may restrict activities such as basketball or cycling
  - NSAIDs, rest, flexibility, isometric strengthening exercises
  - casting if symptoms do not resolve with conservative management
- operative: ossicle excision in refractory cases (patient is skeletally mature with persistent symptoms)

## Congenital Talipes Equinovarus (Club Foot)

### Definition
- congenital foot deformity
- muscle contractures resulting in CAVE deformity
- bony deformity: talar neck medial and plantar deviated; varus calcaneus and rotated medially around talus; navicular and cuboid medially displaced

### Etiology
- intrinsic causes (neurologic, muscular, or connective tissue diseases) vs. extrinsic (intrauterine growth restriction); may be idiopathic, neurogenic, or syndrome-associated
- fixed deformity
- 1-2/1000 newborns, 50% bilateral, occurrence M>F, severity F>M

### Physical Exam
- examine hips for associated DDH
- examine knees for deformity
- examine back for dysraphism (unfused vertebral bodies)
- diagnosis is often from physical exam findings alone, radiographs not always required

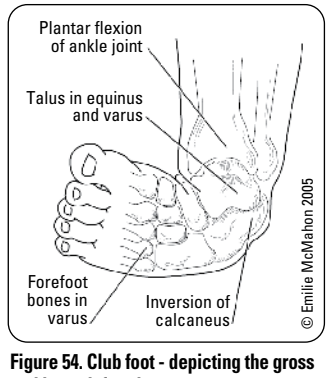



**Figure 54. Club foot - depicting the gross and bony deformity**

**CAVE deformity**
- Midfoot **C**avus
- Forefoot **A**dductus
- Hindfoot **V**arus
- Hindfoot **E**quinus

### Treatment
- largely non-operative via Ponseti Technique (serial manipulation and casting)
  - correct deformities in CAVE order
    - change strapping/cast q1-2wk
    - surgical release in refractory case (rare)
      - delayed until 3-4 mo of age
- 3 yr recurrence rate = 5-10%
- mild recurrence common; affected foot is permanently smaller/stiffer than normal foot with calf muscle atrophy

# Scoliosis

### Definition
- lateral curvature of spine with vertebral rotation
- age: 10-14 yr
- more frequent and more severe in females

### Etiology
- idiopathic: most common (90%)
- congenital: vertebrae fail to form or segment
- neuromuscular: UMN or LMN lesion, myopathy
- postural: leg length discrepancy, muscle spasm
- other: osteochondrodystrophies, neoplastic, traumatic

### Clinical Features
- cosmetic concern ± back pain
- primary curve where several vertebrae affected
- secondary compensatory curves above and below fixed primary curve to try and maintain normal position of head and pelvis
- asymmetric shoulder height when bent forward
- Adam's test: rib hump when bent forward
- prominent scapulae, creased flank, asymmetric pelvis
- associated posterior midline skin lesions in neuromuscular scoliosis
  - café-au-lait spots, dimples, neurofibromas
  - axillary freckling, hemangiomas, hair patches
- associated pes cavus or leg atrophy
- apparent leg length discrepancy

### Investigations
- X-ray: 3-foot standing, AP, lateral
  - measure curvature: Cobb angle
  - may have associated kyphosis

### Treatment
- based on Cobb angle
  - <25°: observe for changes with serial radiographs
  - >25° or progressive: bracing (many types) that halt/slow curve progression but do not reverse deformity
  - >45°, cosmetically unacceptable, or respiratory problems: surgical correction (spinal fusion)

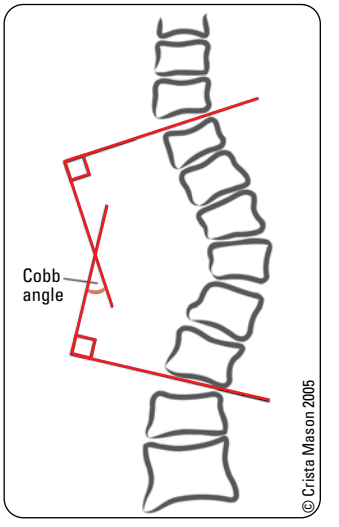



**Figure 55. Cobb angle** – used to monitor the progression of the scoliotic curve

Scoliosis screening is not recommended in Canada (Grieg A, et al. 2010; Health Canada, 1994)

In structural or fixed scoliosis, bending forwards makes the curve more obvious

Postural scoliosis can be corrected by correcting the underlying problem

# Bone Tumours

- primary bone tumours are rare after 3rd decade
- metastases to bone are relatively common after 3rd decade

### Clinical Features
- malignant (primary or metastasis): local pain and swelling (weeks to months), worse on exertion and at night, ± soft tissue mass
- benign: usually asymptomatic
- minor trauma often initiating event that calls attention to lesion

**Red Flags**
- Persistent skeletal pain
- Localized tenderness
- Spontaneous fracture
- Enlarging mass/soft tissue swelling

**X-ray Findings**
- Lytic, lucent, sclerotic bone
- Involvement of cortex, medulla, soft tissue
- Radiolucent, radiopaque, or calcified matrix
- Periosteal reaction
- Permeative margins
- Pathological fracture
- Soft tissue swelling

**Table 25. Distinguishing Benign from Malignant Bone Lesions on X-Ray**

| Benign | Malignant |
|---|---|
| No periosteal reaction | Acute periosteal reaction<br>• Codman's triangle<br>• "Onion skin"<br>• "Sunburst" |
| Thick endosteal reaction<br>Well developed bone formation<br>Intraosseous and even calcification | Broad border between lesion and normal bone<br>Varied bone formation<br>Extraosseous and irregular calcification |

Adapted from: Buckholtz RW, Heckman JD. Rockwood and Green's Fractures in Adults. Volume 1. Philadephia: Lippincott Williams & Wilkins, 2001. p558

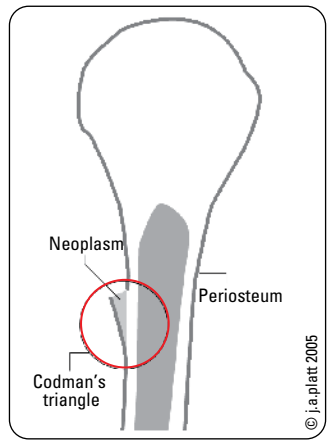



**Figure 56. Codman's triangle** – a radiographic finding in malignancy, where the partially ossified periosteum is lifted off the cortex by neoplastic tissue

### Diagnosis
- malignancy is suggested by rapid growth, warmth, tenderness, lack of sharp definition
- staging should include:
  - blood work including liver enzymes
  - CT chest
  - bone scan
  - bone biopsy
    - should be referred to specialized centre prior to biopsy
    - classified into benign, benign aggressive, and malignant
  - MRI of affected bone

# Benign Active Bone Tumours

## BONE-FORMING TUMOURS

### Osteoid Osteoma
- bone tumour arising from osteoblasts
- peak incidence in 2nd and 3rd decades, M:F = 2:1
- proximal femur and tibia diaphysis most common locations
- not known to metastasize
- radiographic findings: small, round radiolucent nidus (<1.5 cm) surrounded by dense sclerotic bone ("bull's-eye")
- symptoms: produces severe intermittent pain from prostaglandin secretion and COX1/2 expression, mostly at night (diurnal prostaglandin production), thus is characteristically relieved by NSAIDs
- treatment: NSAIDs for night pain; surgical resection of nidus

## FIBROUS LESIONS

### Fibrous Cortical Defect
- i.e. non-ossifying fibroma, fibrous bone lesion
- most common benign bone tumour in children, typically asymptomatic and an incidental finding
- occur in as many as 35% of children, peak incidence between 2-25 yr old, higher prevalence in males
- femur and proximal tibia most common locations, 50% of patients have multiple defects that are usually bilateral, symmetrical
- radiographic findings: diagnostic, metaphyseal eccentric 'bubbly' lytic lesion near physis; thin, smooth/lobulated, well-defined sclerotic margin
- treatment: most lesions resolve spontaneously

### Osteochondroma
- cartilage capped bony tumour
- 2nd and 3rd decades, M:F = 1.8:1
- most common of all benign bone tumours – 45%
- 2 types: sessile (broad based and increased risk of malignant degeneration) vs. pedunculated (narrow stalk)
- metaphysis of long bone near tendon attachment sites (usually distal femur, proximal tibia, or proximal humerus)
- radiographic findings: cartilage-capped bony spur on surface of bone ("mushroom" on x-ray)
- may be multiple (hereditary, autosomal dominant form) – higher risk of malignant change
- generally very slow growing and asymptomatic unless impinging on neurovascular structure ('painless mass')
  - growth usually ceases when skeletal maturity is reached
- malignant degeneration occurs in 1-2% (becomes painful or rapidly grows)
- treatment: typically observation; surgical excision if symptomatic

### Enchondroma
- hyaline cartilage tumour; majority asymptomatic, presenting as incidental finding or pathological fracture
- 2nd and 3rd decades
- 60% occur in the small tubular bones of the hand and foot; others in femur (20% - Figure 57), humerus, ribs
- benign cartilaginous growth, an abnormality of chondroblasts, develops in medullary cavity
  - single/multiple enlarged rarefied areas in tubular bones
  - lytic lesion with sharp margination and irregular central calcification (stippled/punctate/popcorn appearance)
- malignant degeneration to chondrosarcoma occurs in 1-2% (pain in absence of pathologic fracture is an important clue)
- not known to metastasize
- treatment: observation with serial x-rays; surgical curettage if symptomatic or lesion grows



**Figure 57. T1 MRI of femoral enchondroma**

### CYSTIC LESIONS

### Unicameral/Solitary Bone Cyst
- most common cystic lesion; serous fluid-filled lesion
- children and young adults, peak incidence during first 2 decades, M:F = 2:1
- proximal humerus and femur most common
- symptoms: asymptomatic, or local pain; complete pathological fracture (50% of presentations) or incidental detection
- radiographic findings: lytic translucent area on metaphyseal side of growth plate, cortex thinned/expanded; well-defined lesion
- treatment: aspiration followed by steroid injection; curettage ± bone graft indicated if re-fracture likely

## Benign Aggressive Bone Tumours

### Giant Cell Tumours/Aneurysmal Bone Cyst/Osteoblastoma
- affects patients of skeletal maturity, peak 3rd decade
- osteoblastoma: found in the distal femur, proximal tibia, distal radius, sacrum, tarsal bones, spine
- giant cell tumour: pulmonary metastases in 3%
- aneurysmal bone cysts: either solid with fibrous/granular tissue, or blood-filled
- radiographic findings
  - giant cell tumour: eccentric lytic lesions in epiphyses adjacent to subchondral bone; may break through cortex; T2 MRI enhances fluid within lesion (hyper-intense signal)
  - aneurysmal bone cyst: expanded with honeycomb shape
  - osteoblastoma: often nonspecific; calcified central nidus (>2 cm) with radiolucent halo and sclerosis
- symptoms: local tenderness and swelling, pain may be progressive (giant cell tumours), ± symptoms of nerve root compression (osteoblastoma)
- 15% recur within 2 yr of surgery



**Figure 58. X-ray of aneurysmal bone cyst**
Note the aggressive destruction of bone

### Treatment
- intralesional curettage + bone graft or cement
- wide local excision of expendable bones

## Malignant Bone Tumours

**Table 26. Most Common Malignant Tumour Types for Age**

| Age | Tumour |
|---|---|
| <1 | Neuroblastoma |
| 1-10 | Ewing's of tubular bones |
| 10-30 | Osteosarcoma, Ewing's of flat bones |
| 30-40 | Reticulum cell sarcoma, fibrosarcoma, periosteal osteosarcoma, malignant giant cell tumour, lymphoma |
| >40 | Metastatic carcinoma, multiple myeloma, chondrosarcoma |

### Osteosarcoma
- malignant bone tumour
- most frequently diagnosed in 2nd decade of life (60%), 2nd most common primary malignancy in adults
- history of Paget's disease (elderly patients), previous radiation treatment
- predilection for sites of rapid growth: distal femur (45% - Figure 59), proximal tibia (20%), and proximal humerus (15%)
  - invasive, variable histology; frequent metastases without treatment (lung most common)
- painful symptoms: progressive pain, night pain, poorly defined swelling, decreased ROM



**Figure 59. X-ray of osteosarcoma of distal femur**

- radiographic findings
  - characteristic periosteal reaction: Codman's triangle (Figure 56) or "sunburst" spicule formation (tumour extension into periosteum)
  - destructive lesion in metaphysis may cross epiphyseal plate
- management: complete resection (limb salvage, rarely amputation), neo-adjuvant chemo; bone scan – rule out skeletal metastases, CT chest – rule out pulmonary metastases
- prognosis: 90% survival for low-grade; 70% survival for high-grade

### Chondrosarcoma
- malignant chondrogenic tumour
- primary (2/3 cases)
  - previous normal bone, patient >40 yr; expands into cortex to cause pain, pathological fracture
- secondary (1/3 cases)
  - malignant degeneration of pre-existing cartilage tumour such as enchondroma or osteochondroma
  - age range 25-45 yr, better prognosis than primary chondrosarcoma
- symptoms: progressive pain, uncommonly palpable mass
- radiographic findings: in medullary cavity, irregular "popcorn" calcification
- treatment: unresponsive to chemotherapy, treat with aggressive surgical resection + reconstruction; regular follow-up X-rays of resection site and chest
- prognosis: 90% survival for low-grade (10yr survival); 20-40% survival for high-grade

### Ewing's Sarcoma
- malignant, small round cell sarcoma
- most occur between 5-25 yr old
- florid periosteal reaction in metaphyses of long bone with diaphyseal extension
- metastases frequent without treatment
- signs/symptoms: presents with pain, mild fever, erythema, and swelling; anemia, increased WBC, ESR, LDH (mimics an infection)
- radiographic findings: moth-eaten appearance with periosteal lamellated pattern ("onion-skinning")
- treatment: resection, chemotherapy, radiation
- prognosis: 70% survival, worst prognostic factor is distant metastases

### Multiple Myeloma
- proliferation of neoplastic plasma cells
- most common primary malignant tumour of bone in adults (~43%)
- 90% occur in people >40 yr old, M:F = 2:1; twice as common in African-Americans
- signs/symptoms: localized bone pain (cardinal early symptom), compression/pathological fractures, renal failure, nephritis, high incidence of infections (e.g. pyelonephritis/pneumonia), systemic (weakness, weight loss, anorexia)
- labs: anemia, thrombocytopenia, increased ESR, hypercalcemia, increased Cr
- radiographic findings: multiple, "punched-out" well-demarcated lesions, no surrounding sclerosis, marked bone expansion
- diagnosis
  - serum/urine immunoelectrophoresis (monoclonal gammopathy)
  - CT-guided biopsy of lytic lesions at multiple bony sites
- treatment: chemotherapy, bisphosphonates, radiation, surgery for symptomatic lesions or impending fractures – debulking, internal fixation
- prognosis: 5 yr survival 30%; 10 yr survival 11%
- see Hematology, H49

### Bone Metastases
- most common cause of bone lesions in adults; typically age >40
- 2/3 from breast or prostate; also consider thyroid, lung, kidney
- usually osteolytic; prostate occasionally osteoblastic
- may present with mechanical pain and/or night pain, pathological fracture, hypercalcemia
- bone scan for MSK involvement, MRI for spinal involvement may be helpful
- treatment: pain control, bisphosphonates, stabilization of impending fractures if Mirel's Critera >8 (ORIF, IM rod, bone cement)

**Table 27. Mirel's Criteria for Impending Fracture Risk and Prophylactic Internal Fixation**

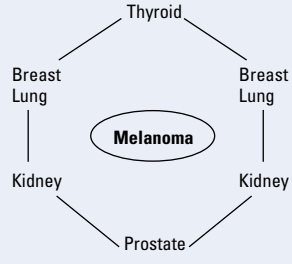
| Variable | Number Assigned | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| **Site** | Upper arm | Lower extremity | Peritrochanteric |
| **Pain** | Mild | Moderate | Severe |
| **Lesion** | Blastic | Mixed | Lytic |
| **Size** | <1/3 bone diameter | 1/3-2/3 diameter | >2/3 diameter |



**Figure 60. X-ray of femur chondrosarcoma**

**Signs of Hypercalcemia**
"Bones, Stones, Moans, Groans, Psychiatric overtones"
CNS: headache, confusion, irritability, blurred vision
GI: N/V, abdominal pain, constipation, weight loss
MSK: fatigue, weakness, unsteady gait, bone and joint pain
GU: nocturia, polydipsia, polyuria, UTIs

**Most Common Tumours Metastatic to Bone**




**BLT with a Kosher Pickle**
**B**reast
**L**ung
**T**hyroid
**K**idney
**P**rostate

# Common Medications

**Table 28. Common Medications**

| Drug Name | Dosing Schedule | Indications | Comments |
|---|---|---|---|
| **cefazolin (Ancef®)** | 1-2 g IV q8h | Pre-operative antibiotic prophylaxis | First generation cephalosporin; do not use with penicillin allergy |
| **heparin** | 5000 IU SC q12h | DVT prophylaxis | Monitor platelets, follow PTT which should rise 1.5-2x |
| **LMWH**<br>dalteparin (Fragmin®)<br>enoxaparin (Lovenox®)<br>fondaparinux (Arixtra®) | 5000 IU SC OD<br>30-40 mg SC bid<br>2.5 mg SC OD | DVT prophylaxis | Fixed dose, no monitoring, improved bioavailability, increased bleeding rates |
| **oral anticoagulants**<br>dabigatran (Pradaxa®)<br>rivaroxaban (Xarelto®)<br>apixaban | 110 mg PO x1 then 220 mg PO OD<br>10 mg PO OD<br>2.5 mg PO bid | DVT prophylaxis | Predictable, no monitoring, oral administration; no antidote |
| **tranexamic acid (TXA)** | 10-20 mg/kg IV<br>Topical application to wound | Reduce perioperative blood loss and transfusion | No evidence for increase in thromboembolic events |
| **midazolam (Versed®)** | 0.02-0.04 mg/kg IV | Conscious sedation for short procedures | Medication used during fracture reduction – monitor for respiratory depression |
| **fentanyl (Sublimaze®)** | 0.5-3 µg/kg IV | IV anesthetic | Short acting anesthetic used in conjunction with midazolam (Versed®) |
| **propofol (Diprivan®)** | 1-2 mg/kg IV<br>Maintenance 0.5 mg/kg | IV anesthetic | Short acting anesthetic often used in conjunction with fentanyl (Sublimaze®) |
| **ibuprofen (Advil®, Motrin®)** | 200-400 mg tid | Analgesia for inflammatory pain (arthritis) | NSAID, may cause gastric erosion and bleeding |
| **triamcinolone (Aristocort®) – an injectable steroid** | 0.5-1 mL of 25 mg/mL | Suspension (injected into inflamed joint or bursa); amount varies by joint size | Potent anti-inflammatory effect;increased pain for 24 h, rarely causes fat necrosis and skin depigmentation |
| **naproxen (Aleve®, Naprosyn®)** | 250-500 mg bid | Analgesia for pain due to inflammation, arthritis, soft tissue injury | NSAID, may cause gastric erosion and bleeding |
| **celecoxib (Celebrex®)** | 200 mg PO bid | Component of multimodal pain control and prophylaxis of HO after THA | NSAID (COX-2 inbibitor), cardiotoxic |
| **misoprostol (Cytotec®)** | 200 µg qid | Prophylaxis of HO after THA | Use with indomethacin |
| **indomethacin (Indocid®)** | 25 mg PO tid | Prophylaxis of HO after THA | Use with misoprostol |

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Notes

# OT Otolaryngology – Head & Neck Surgery

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# Acronyms

| | |
|---|---|
| ABR | auditory brainstem response |
| AC | air conduction |
| AOM | acute otitis media |
| BAHA | bone anchored hearing aid |
| BC | bone conduction |
| C&S | culture and sensitivity |
| CHL | conductive hearing loss |
| CMV | cytomegalovirus |
| CPA | cerebellopontine angle |
| DM | diabetes mellitus |
| EAC | external auditory canal |
| EBV | Epstein-Barr virus |
| FAP | familial adenomatous polyposis |
| FESS | functional endoscopic sinus surgery |
| FNA | fine needle aspiration |
| GERD | gastroesophageal reflux disease |
| GPA | granulomatosis with polyangiitis |
| H&N | head and neck |
| HL | hearing loss |
| HPV | human papillomavirus |
| HSV | herpes simplex virus |
| INCS | intranasal corticosteroids |
| MEE | middle ear effusion |
| MEI | middle ear inflammation |
| MS | multiple sclerosis |
| N/V | nausea/vomiting |
| OE | otitis externa |
| OME | otitis media with effusion |
| OSA | obstructive sleep apnea |
| PMN | polymorphonuclear leukocytes |
| RA | rheumatoid arthritis |
| RSV | respiratory syncytial virus |
| SCC | squamous cell carcinoma |
| SCM | sternocleidomastoid |
| SNHL | sensorineural hearing loss |
| SRT | speech reception threshold |
| TEF | tracheoesophageal fistula |
| TM | tympanic membrane |
| TMJ | temporomandibular joint |
| TMP-SMX | trimethoprim/sulfamethoxazole |
| TNM | tumour, node, metastases |
| URTI | upper respiratory tract infection |

# Basic Anatomy Review

## Ear

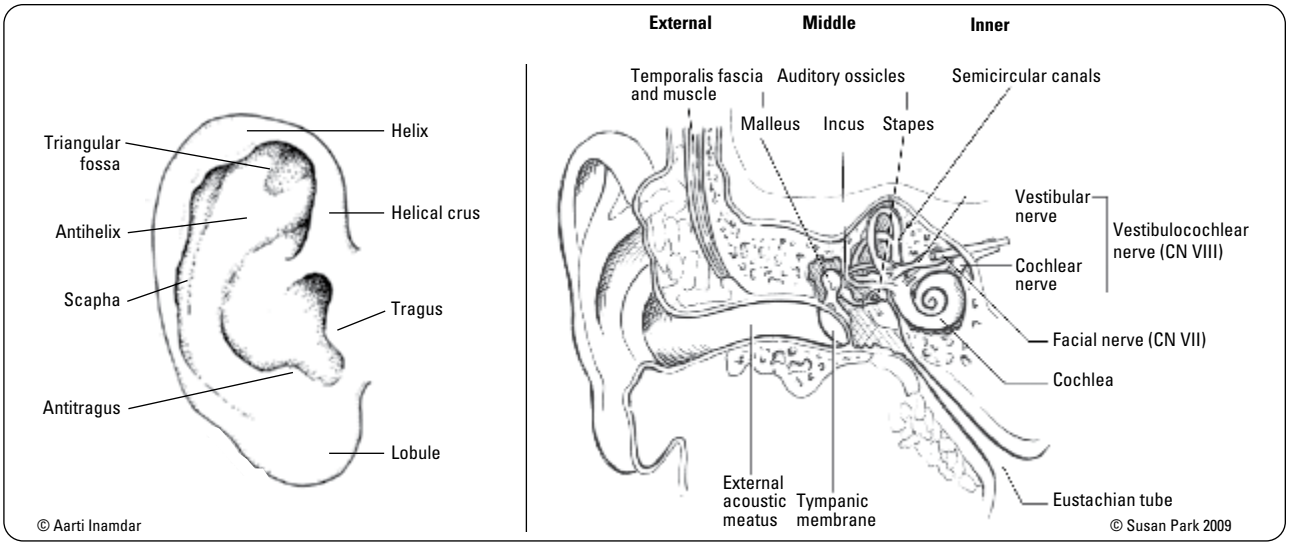



**Figure 1. Surface anatomy of the external ear; anatomy of ear**

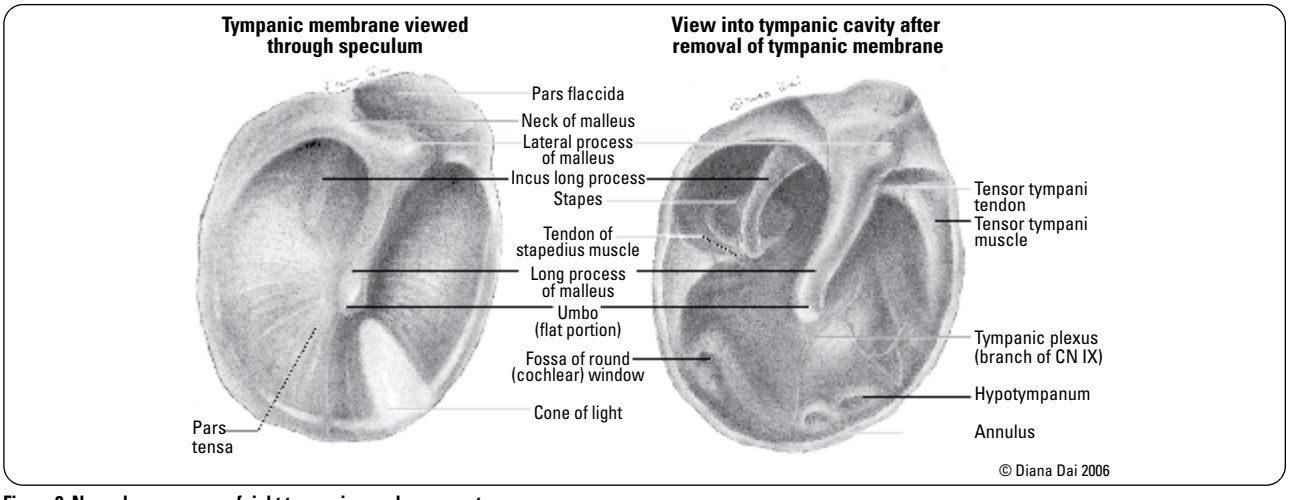



**Figure 2. Normal appearance of right tympanic membrane on otoscopy**

# Nose

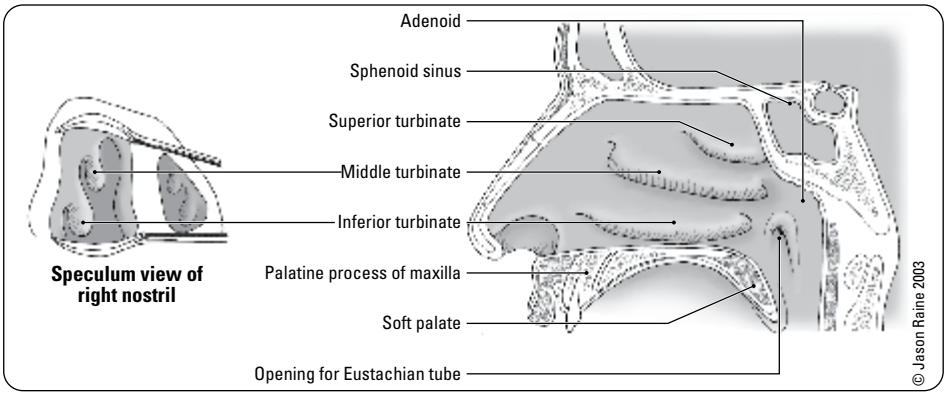



**Figure 3. Nasal anatomy**

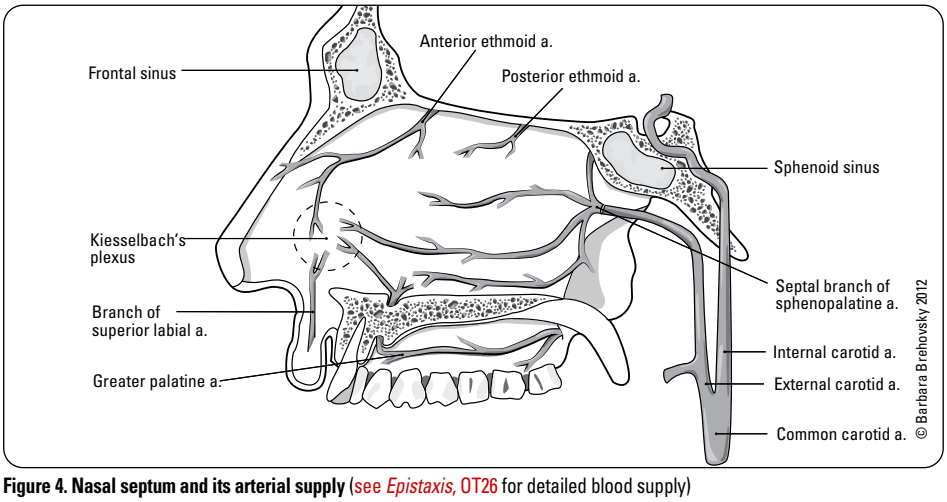



**Figure 4. Nasal septum and its arterial supply** (see *Epistaxis*, OT26 for detailed blood supply)

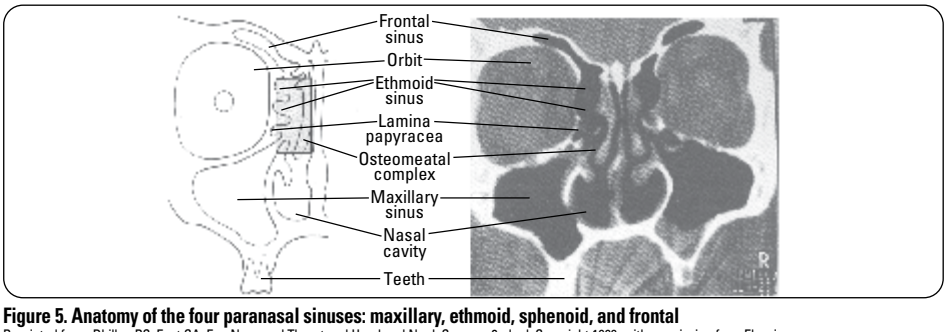



**Figure 5. Anatomy of the four paranasal sinuses: maxillary, ethmoid, sphenoid, and frontal**
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# Throat

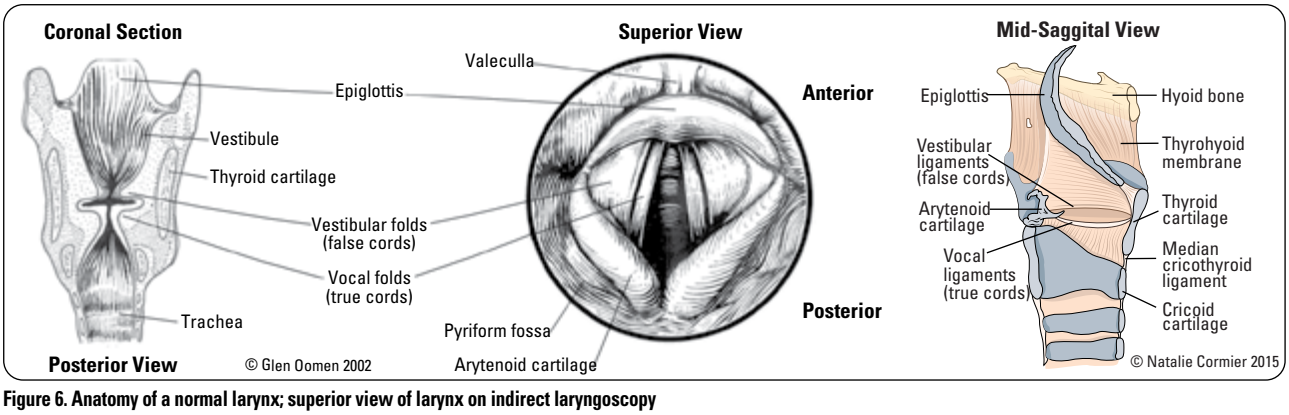



**Figure 6. Anatomy of a normal larynx; superior view of larynx on indirect laryngoscopy**

# Head and Neck

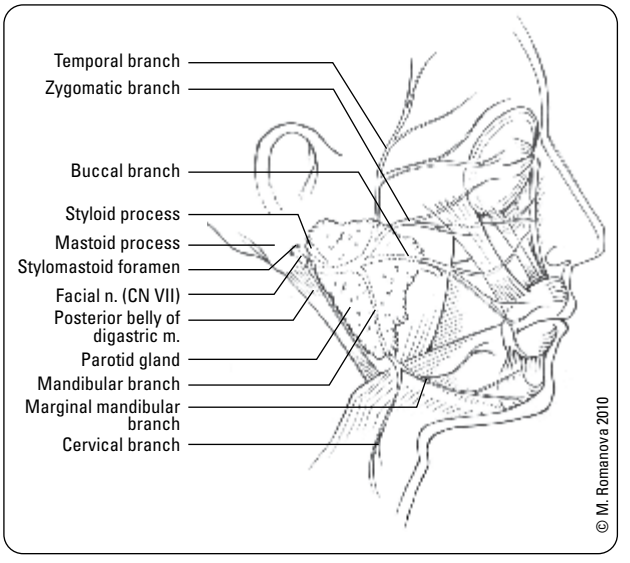



**Figure 7. Extratemporal segment of facial nerve**
**Branches of facial nerve** (in order from superior to inferior)
**T**o **Z**anzibar **B**y **M**otor **C**ar

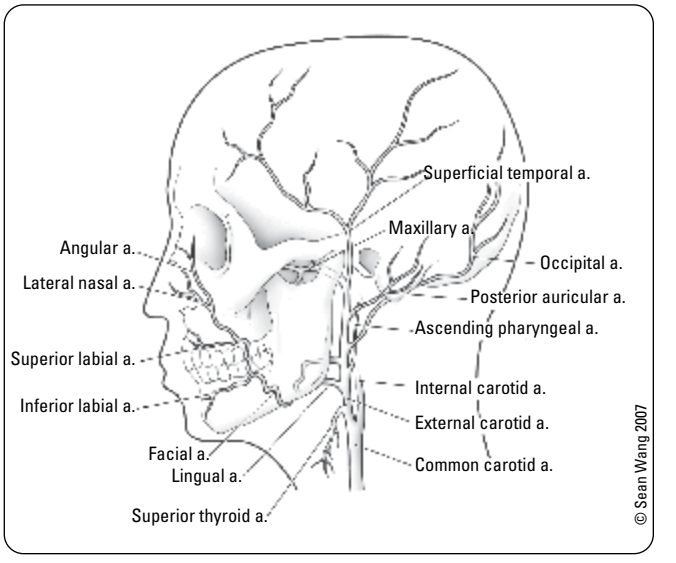



**Figure 8. Blood supply to the face**
**Branches of the external carotid artery** (in order from inferior to superior)
**S**ome **A**natomists **L**ike **F**reaking **O**ut **P**oor **M**edical **S**tudents

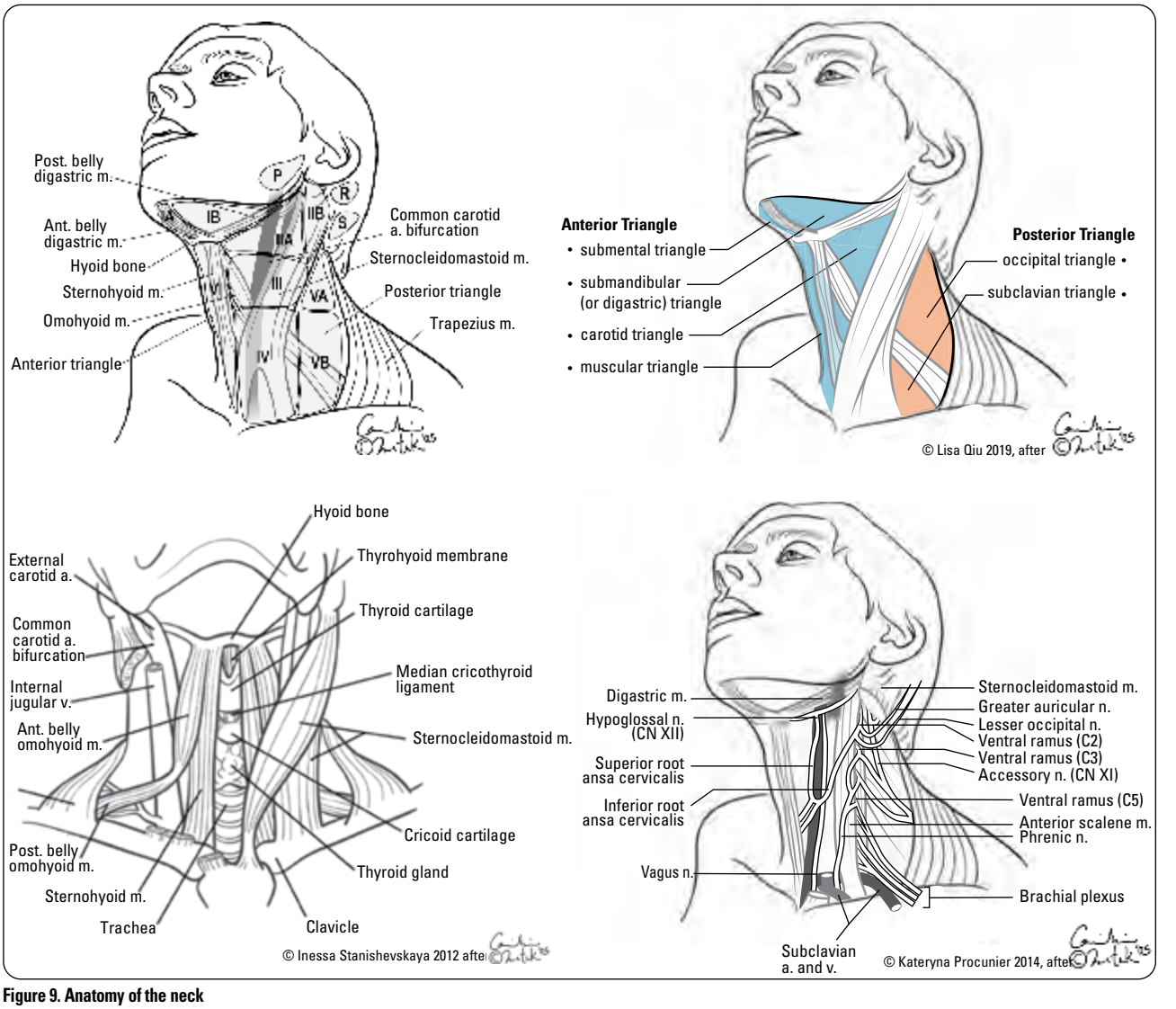



**Figure 9. Anatomy of the neck**

# Anatomical Triangles of the Neck

**Anterior triangle**
- bounded by anterior border of SCM, midline of neck, and lower border of mandible
- divided into:
  - **submental triangle**: bounded by both anterior belly of digastric and hyoid bone
  - **digastric triangle**: bounded by anterior and posterior bellies of digastric and inferior border of mandible
  - **carotid triangle**: bounded by SCM, anterior belly of omohyoid, and posterior belly of digastric
    - contains: tail of parotid, submandibular gland, hypoglossal nerve, carotid bifurcation, and lymph nodes

**Posterior triangle**
- bounded by posterior border of SCM, anterior border of trapezius, and middle third of clavicle
- divided into:
  - **occipital triangle**: superior to posterior belly of the omohyoid
  - **subclavian triangle**: inferior to posterior belly of omohyoid
- contains: spinal accessory nerve and lymph nodes

**Table 1. Lymphatic Drainage of Nodal Groups and Anatomical Triangles of Neck**

| Nodal Group/Level | Location | Drainage |
|---|---|---|
| **1. Suboccipital (S)** | Base of skull, posterior | Posterior scalp |
| **2. Retroauricular (R)** | Superficial to mastoid process | Scalp, temporal region, external auditory meatus, posterior pinna |
| **3. Parotid-preauricular (P)** | Anterior to ear | External auditory meatus, anterior pinna, soft tissue of frontal and temporal regions, root of nose, eyelids, palpebral conjunctiva |
| **4. Submental (Level IA)** | Anterior bellies (midline) of digastric muscles, tip of mandible, and hyoid bone | Floor of mouth, anterior tongue, anterior mandibular alveolar ridge, lower lip |
| **5. Submandibular (Level IB)** | Anterior belly of digastric muscle, stylohyoid muscle, body of mandible | Oral cavity, anterior nasal cavity, soft tissues of the mid-face, submandibular gland |
| **6. Upper jugular (Levels IIA and IIB)** | Skull base to inferior border of hyoid bone along SCM muscle | Oral cavity, nasal cavity, naso/oro/hypopharynx, larynx, parotid glands |
| **7. Middle jugular (Level III)** | Inferior border of hyoid bone to inferior border of cricoid cartilage along SCM muscle | Oral cavity, naso/oro/hypopharynx, larynx |
| **8. Lower jugular* (Level IV)** | Inferior border of cricoid cartilage to clavicle along SCM muscle | Hypopharynx, thyroid, cervical esophagus, larynx |
| **9. Posterior triangle** (Levels VA and VB)** | Posterior border of SCM, anterior border of trapezius, from skull base to clavicle | Nasopharynx and oropharynx, cutaneous structures of the posterior scalp and neck |
| **10. Anterior compartment*** (Level VI)** | Hyoid bone (midline) to suprasternal notch between the common carotid arteries | Thyroid gland, glottic and subglottic larynx, apex of piriform sinus, cervical esophagus |

*Virchow node: left lower jugular (level IV) supraclavicular node
**Includes some supraclavicular nodes
***Includes pretracheal, precricoid, paratracheal, and perithyroidal nodes

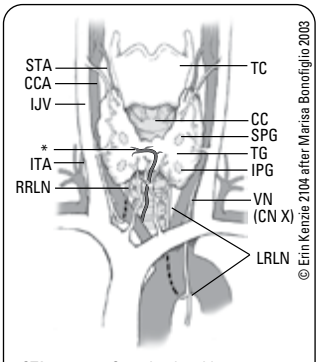
**Paired Parasympathetic Ganglia of the Head and Neck**
- **Ciliary:** pupillary constriction
- **Pterygopalatine:** lacrimal gland, nasal mucosa
- **Submandibular:** submandibular, sublingual glands
- **Otic:** parotid gland

**Function of Facial Nerve**

**"Ears, Tears, Face, Taste"**
**Ears:** stapedius muscle
**Tears:** lacrimation (lacrimal gland) and salivation
**Face:** muscles of facial expression
**Taste:** sensory anterior 2/3 of tongue (via chorda tympani)

- **Left-sided** enlargement of a supraclavicular node (Virchow's node) may indicate an abdominal malignancy or malignancy below the clavicle
- **Right-sided** enlargement may indicate malignancy of the mediastinum, lungs, or esophagus
- **Occipital and/or posterior auricular node** enlargement may indicate rubella

**4 Strap Muscles of the Neck**
- Thyrohyoid
- Omohyoid
- Sternohyoid
- Sternothyroid




STA – Superior thyroid artery
CCA – Common carotid artery
IJV – Internal jugular vein
ITA – Inferior thyroid artery
RRLN – Right recurrent laryngeal nerve
TC – Thyroid cartilage
CC – Cricoid cartilage
SPG – Superior parathyroid gland
TG – Thyroid gland
IPG – Inferior parathyroid gland
VN (CN X) – Vagus nerve (CN X)
LRLN – Left recurrent laryngeal nerve

*Thyroidea ima artery: present in 3% of population, arises from aortic arch or innominate artery

**Figure 10. Anatomy of the thyroid gland**

# Differential Diagnoses of Common Presentations

## Dizziness

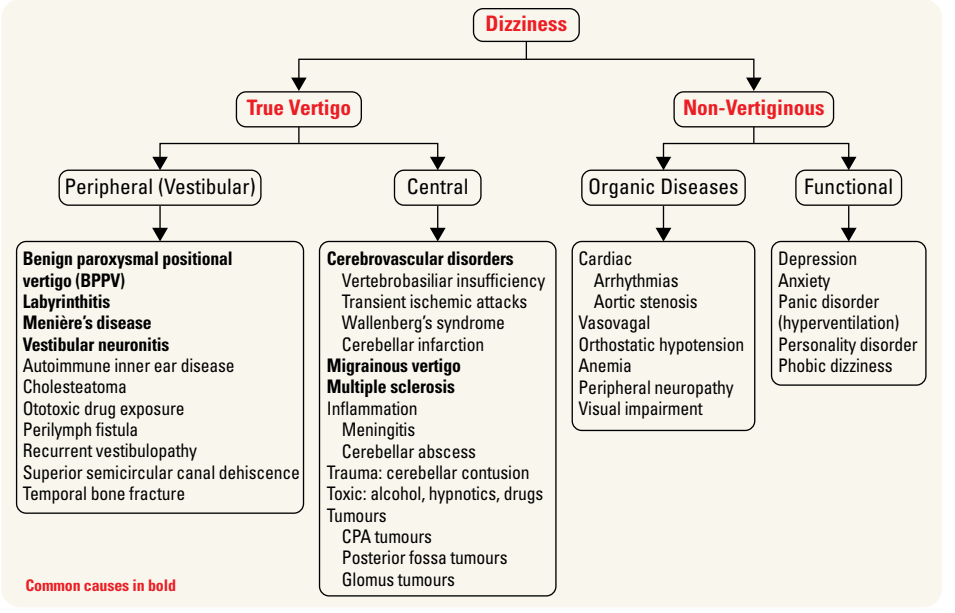



**Figure 11. Differential diagnosis of dizziness**

True nystagmus and vertigo caused by a peripheral lesion will never last longer than a few weeks, due to compensation from the cerebellum (unless there is a history of cerebellar ischemia/stroke). Central lesions do not compensate, therefore nystagmus and vertigo will persist

**5 "D"s of Vertebrobasilar Insufficiency**
**D**rop attacks
**D**iplopia
**D**ysarthria
**D**izziness
**D**ysphagia

## Otalgia

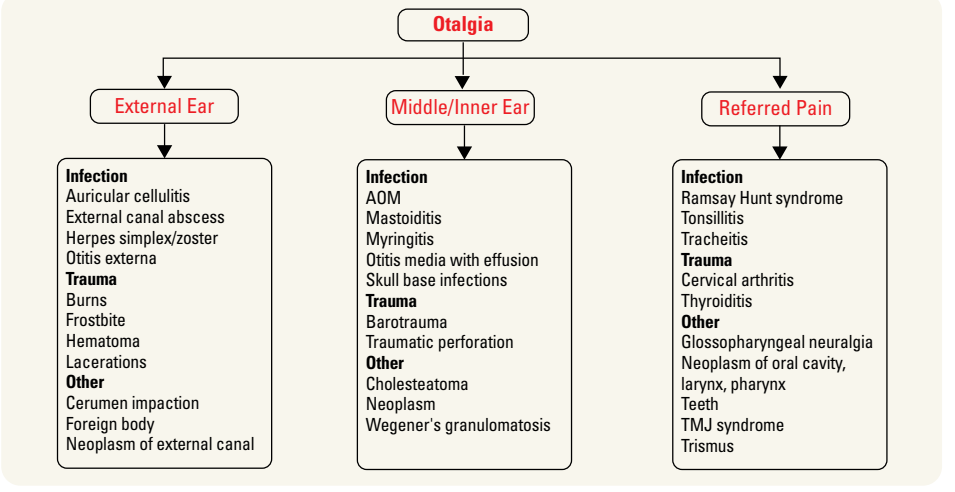



**Figure 12. Differential diagnosis of otalgia**

# Hearing Loss

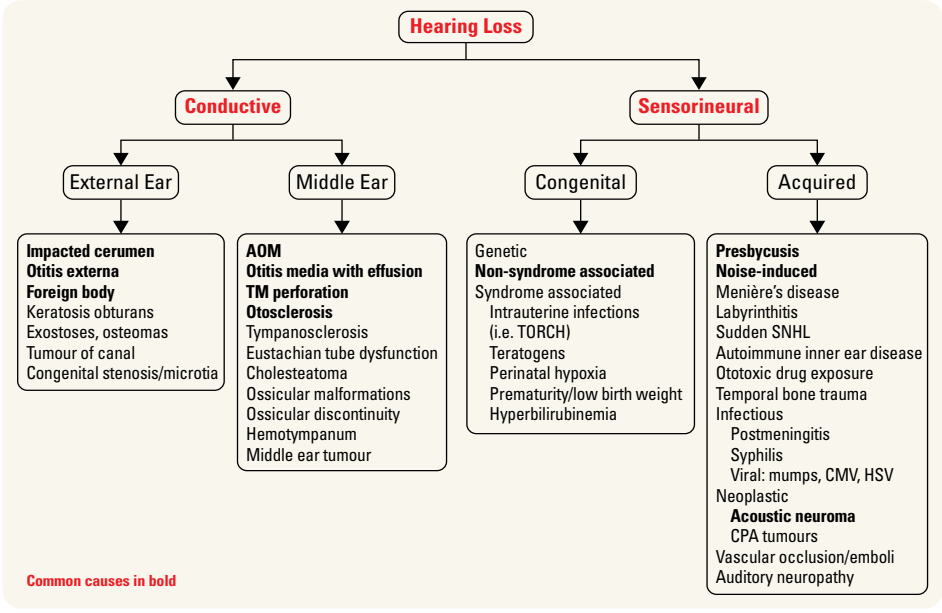



**Figure 13. Differential diagnosis of hearing loss**

# Tinnitus

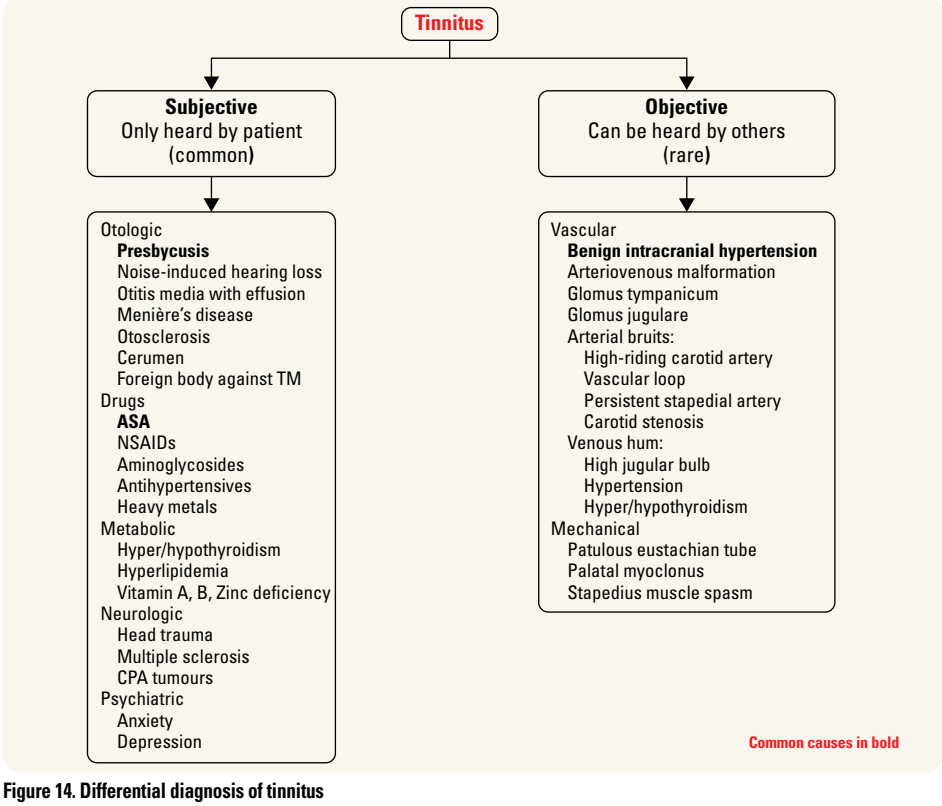



**Figure 14. Differential diagnosis of tinnitus**

Tinnitus is most commonly associated with SNHL

**Glomus Tympanicum/Jugulare Tumour Signs and Symptoms**

- Pulsatile tinnitus
- Hearing loss
- Blue mass behind TM
- Brown's sign (blanching of the TM with pneumatic otoscopy)

# Nasal Obstruction

**Table 2. Differential Diagnosis of Nasal Obstruction**

| Acquired | Congenital |
|---|---|
| **Nasal Cavity**<br>Rhinitis<br>Acute/chronic<br>Vasomotor<br>Allergic<br>Rhinosinusitis<br>Foreign bodies<br>Enlarged turbinates<br>Tumour<br>Benign: polyps, inverting papilloma<br>Malignant<br>SCC<br>Esthesioneuroblastoma (olfactory neuroblastoma)<br>Adenocarcinoma | **Nasal Cavity**<br>Nasal dermoid cyst<br>Encephalocele<br>Glioma<br>Choanal atresia |
| **Nasal Septum**<br>Septal deviation<br>Septal hematoma/abscess<br>Dislocated septum | **Nasal Septum**<br>Septal deviation<br>Septal hematoma/abscess<br>Dislocated septum |
| **Nasopharynx**<br>Adenoid hypertrophy<br>Tumour<br>Benign: juvenile nasopharyngeal angiofibroma (JNA), polyps<br>Malignant: nasopharyngeal carcinoma | |
| **Systemic** | |
| Granulomatous diseases, diabetes, vasculitis | |

# Hoarseness

**Table 3. Differential Diagnosis of Hoarseness**

| | | |
|---|---|---|
| **Infectious** | Acute/chronic laryngitis<br>Laryngotracheobronchitis (croup) | |
| **Inflammatory** | GERD<br>Vocal cord polyps/nodules<br>Lifestyle: smoking, chronic EtOH use | |
| **Trauma** | External laryngeal trauma<br>Endoscopy and endotracheal tube (e.g. intubation granuloma) | |
| **Neoplasia** | Benign tumour<br>Papillomas (HPV infection)<br>Minor salivary gland tumours<br>Other | Malignant tumours (e.g. thyroid)<br>SCC<br>Other |
| **Cysts** | Retention cysts | |
| **Systemic** | Endocrine<br>Hypothyroidism<br>Virilization | Connective tissue disease<br>RA<br>SLE |
| **Neurologic** (vocal cord paralysis due to superior ± recurrent laryngeal nerve injury) | Central lesions<br>Cerebrovascular accident (CVA)<br>Head injury<br>Multiple sclerosis (MS)<br>Skull base tumours<br>Arnold-Chiari malformation<br>Peripheral lesions<br>Unilateral<br>Lung malignancy | Iatrogenic injury: thyroid, parathyroid surgery, carotid endarterectomy, patent ductus arteriosus (PDA) ligation<br>Bilateral<br>Iatrogenic injury: bilateral thyroid surgery, forceps delivery<br>Neuromuscular<br>Myasthenia gravis |
| **Functional** | Psychogenic aphonia (hysterical aphonia) | |
| **Congenital** | Laryngomalacia<br>Laryngeal web<br>Laryngeal atresia | |



Lung malignancy is the most common cause of extralaryngeal vocal cord paralysis

# Neck Mass

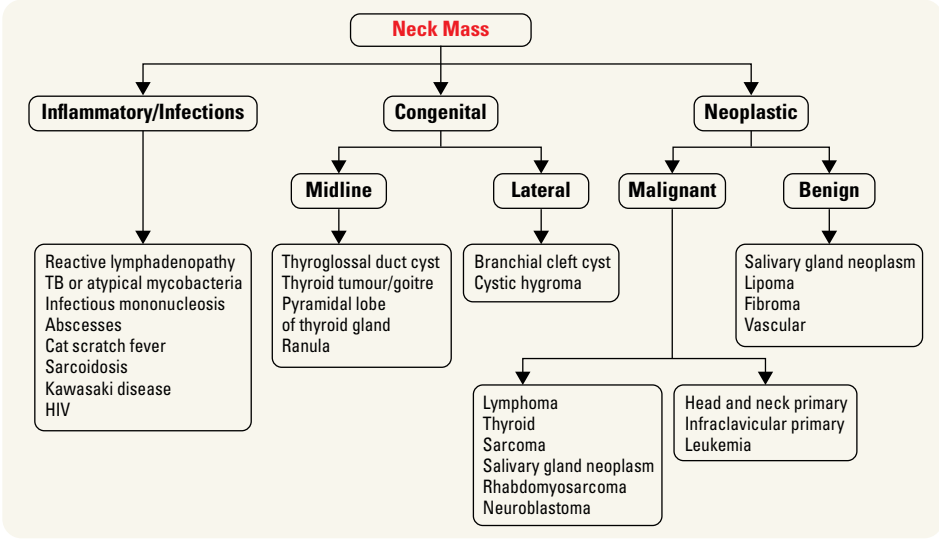



**Figure 15. Differential diagnosis of a neck mass**

# Hearing

## Normal Hearing Physiology

- **conductive pathway** (EAC to cochlea): air conduction of sound down the EAC → vibration of TM → sequential vibration of middle ear ossicles (malleus, incus, stapes) → transmission of amplified vibrations from stapes footplate to the oval window of the cochlea → transmitted vibrations via cochlear fluid create movement along the basilar membrane within the cochlea
- **neural pathway** (nerve to brain): basilar membrane vibration stimulates overlying hair cells in the organ of Corti → stimulation of bipolar neurons in the spiral ganglion of the cochlear division of CN VIII → cochlear nucleus → superior olivary nucleus → lateral lemniscus → inferior colliculus → Sylvian fissure of temporal lobe

**Order of the Neural Pathway (with corresponding waves on ABR)**

**E COLI**
**E**ighth cranial nerve (I – II)
**C**ochlear nucleus (III)
Superior **O**livary nucleus
**L**ateral leminiscus (IV – V)
**I**nferior colliculus

## Types of Hearing Loss

### 1. Conductive Hearing Loss
- conduction of sound to the cochlea is impaired
- can be caused by external and middle ear disease

### 2. Sensorineural Hearing Loss
- defect in the conversion of sound into neural signals or in the transmission of those signals to the cortex
- can be caused by disease of the inner ear (cochlea), acoustic nerve (CN VIII), brainstem, or cortex

### 3. Mixed Hearing Loss
- combination of CHL and SNHL

### Auditory Acuity
- whispered-voice test: mask one ear and whisper into the other
- tuning fork tests (see Table 4; audiogram is of greater utility)
  - Rinne test
    - 512 Hz tuning fork is struck and held firmly on mastoid process to test bone conduction (BC); the tuning fork is then placed beside the pinna to test air conduction (AC)
    - if AC > BC → positive Rinne (normal)
  - Weber test
    - 512 Hz tuning fork is held on vertex of head and patient states whether it is heard centrally (Weber negative) or is lateralized to one side (Weber right, Weber left)
    - can place vibrating fork on patient's chin while they clench their teeth, or directly on teeth to elicit more reliable response
    - will only lateralize if difference in hearing loss between ears is >6 dB

Weber Test lateralization = ipsilateral conductive hearing loss or contralateral sensorineural hearing loss

The Weber test is more sensitive in detecting CHL than the Rinne test

**Table 4. The Interpretation of Tuning Fork Tests**

| Examples | Weber | Rinne |
|---|---|---|
| Normal or bilateral SNHL | Central | AC>BC (+) bilaterally |
| Right-sided CHL, normal left ear | Lateralizes to right | BC>AC (–) right |
| Right-sided SNHL, normal left ear | Lateralizes to left | AC>BC (+) bilaterally |
| Right-sided severe SNHL or dead right ear, normal left ear | Lateralizes to left | BC>AC (–) right* |

*A vibrating tuning fork on the mastoid stimulates the cochlea bilaterally, therefore in this case the left cochlea is stimulated by the Rinne test on the right (e.g. a false negative test). These tests are not valid if the ear canals are obstructed with cerumen (e.g. will create conductive loss)

| Frequency of Tuning Fork (Hz) | Minimum Hearing Loss for Rinne to Reverse (BC>AC, NEGATIVE Rinne) (dB) |
|---|---|
| 256 | 15 |
| 512 | 30 |
| 1024 | 45 |

# Pure Tone Audiometry

- a threshold is the lowest intensity level at which a patient can hear the tone 50% of the time
- thresholds are obtained for each ear at frequencies of 250, 500, 1000, 2000, 4000, and 8000 Hz
- air conduction thresholds are obtained with headphones and measure outer, middle, inner ear, and auditory nerve function
- bone conduction thresholds are obtained with bone conduction oscillators which bypass the outer and middle ear

**Range of Frequencies Audible to Human Ear**
- 20 to 20000 Hz
- Most sensitive frequencies: 1000 to 4000 Hz
- Range of human speech: 500 to 2000 Hz

## Degree of Hearing Loss

- determined on basis of the pure tone average (PTA) at 500, 1000, and 2000 Hz

Hearing loss most often occurs at higher frequencies. Noise-induced (occupational) HL is classically seen at 4000 Hz (Boilermaker's notch). HL associated with otosclerosis is seen at 2000 Hz (Carhart's notch)

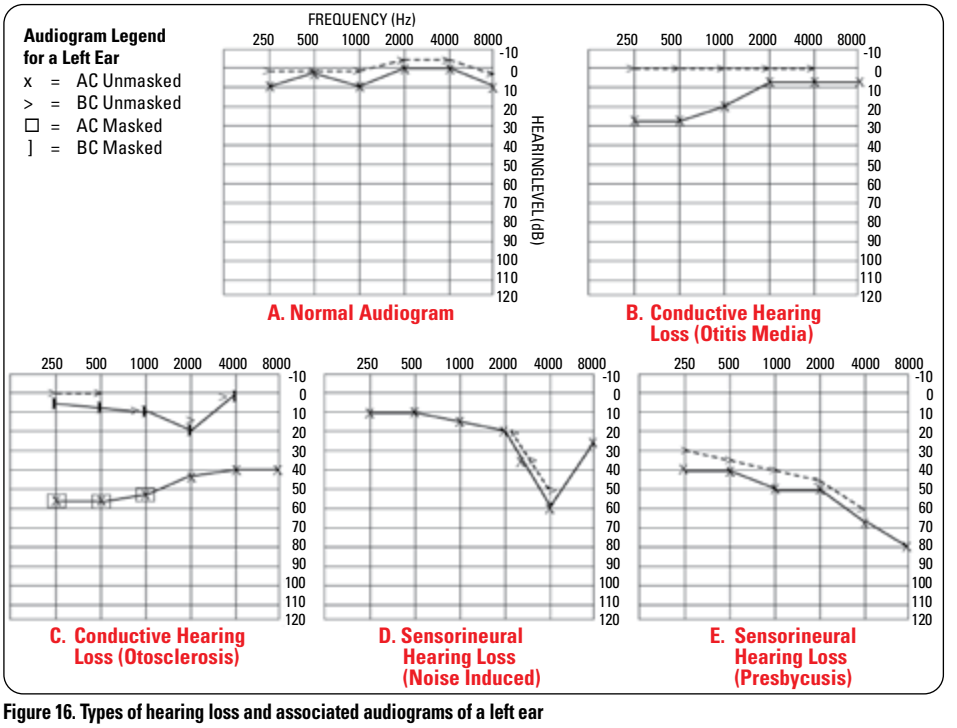



**Figure 16. Types of hearing loss and associated audiograms of a left ear**

## PURE TONE PATTERNS

### 1. Conductive Hearing Loss (Figure 16B and 16C)
- BC in normal range
- AC outside of normal range
- gap between AC and BC thresholds >10 dB (an air-bone gap)

### 2. Sensorineural Hearing Loss (Figure 16D and 16E)
- both air and bone conduction thresholds below normal
- gap between AC and BC <10 dB (no air-bone gap)

### 3. Mixed Hearing Loss
- both air and bone conduction thresholds below normal
- gap between AC and BC thresholds >10 dB (an air-bone gap)

# Speech Audiometry

### Speech Reception Threshold
- lowest hearing level at which patient is able to repeat 50% of two syllable words which have equal emphasis on each syllable (spondee words)
- speech reception threshold (SRT) and best pure tone threshold in the 500 to 2000 Hz range (frequency range of human speech) usually agree within 5 dB; if not, suspect a retrocochlear lesion or functional hearing loss
- used to assess the reliability of the pure tone audiometry

### Speech Discrimination Test
- percentage of words the patient correctly repeats from a list of 50 monosyllabic words
- tested at 40 dB above the patient's SRT, therefore degree of hearing loss is taken into account
- patients with normal hearing or CHL score >90%
- rollover effect: a decrease in discrimination as sound intensity increases; typical of a retrocochlear lesion (e.g. acoustic neuroma)
- investigate further if scores differ more than 20% between ears, as asymmetry may indicate a retrocochlear lesion
- best predictor of hearing aid response: a poor discrimination score indicates significant neural degeneration and hearing aids may not be the best option for the patient

# Impedance Audiometry

### Tympanogram
- the Eustachian tube equalizes the pressure between the external and middle ear
- tympanograms graph the compliance of the middle ear system against a pressure gradient ranging from −400 to +200 mm$H_2O$
- tympanogram peak occurs at the point of maximum compliance: where the pressure in the external canal is equivalent to the pressure in the middle ear
- normal range: −100 to +50 mm$H_2O$

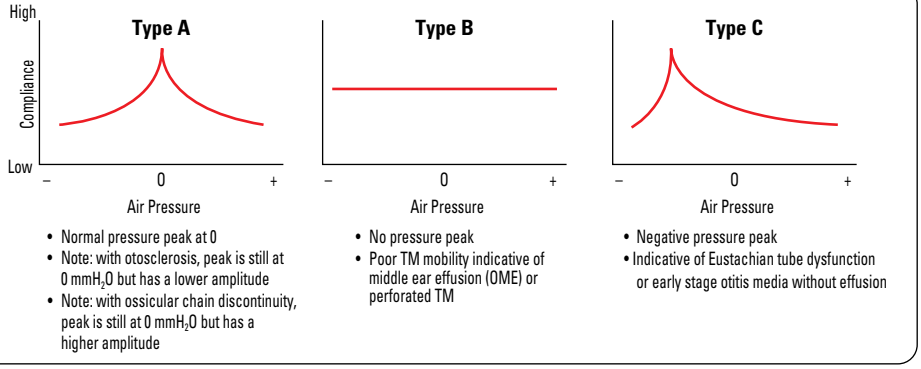



**Figure 17. Tympanograms**

### Static Compliance
- volume measurement reflecting overall stiffness of the middle ear system
- normal range: 0.3-1.6 cc
- negative middle ear pressure and abnormal compliance indicate middle ear pathology
- in a type B curve, ear canal volumes of >2 cc in children and >2.5 cc in adults indicate TM perforation or presence of a patent ventilation tube

### Acoustic Stapedial Reflexes
- stapedius muscle contracts in response to loud sound
- acoustic reflex threshold = 70-100 dB greater than hearing threshold; if hearing threshold >85 dB, reflex likely absent
  - stimulating either ear causes bilateral and symmetrical reflexes
  - for reflex to be present, CN VII must be intact with no CHL in monitored ear
  - if reflex is absent without CHL or severe SNHL, suspect CN VII lesion
- **acoustic reflex decay test** = ability of stapedius muscle to sustain contraction for 10 s at 10 dB
  - normally, little reflex decay occurs at 500 and 1000 Hz
- with cochlear hearing loss, acoustic reflex thresholds are 25-60 dB
- with retrocochlear hearing loss (acoustic neuroma), absent acoustic reflexes or marked reflex decay (>50%) within 5 s

## Auditory Brainstem Response

- measures neuroelectric potentials (waves) in response to a stimulus in five different anatomic sites (see Order of Neural Pathway sidebar on OT9; this test can be used to determine the site of lesion)
- delay in brainstem response suggests cochlear or retrocochlear abnormalities
- does not require volition or co-operation of patient (therefore, of value in children and malingerers)

## Otoacoustic Emissions

- objective test of hearing where a series of clicks is presented to the ear and the cochlea generates an echo which can be measured
- often used in newborn screening
- can be used to uncover normal hearing in malingering patients
- absence of emissions can be due to hearing loss or fluid in the middle ear



Pre-lingually deaf infants are the best candidates for aural rehabilitation because they have maximal benefit from ongoing developmental plasticity

## Aural Rehabilitation

- dependent on degree of hearing loss, communicative requirements, motivation, expectations, and physical and mental abilities
- negative prognostic factors
  - poor speech discrimination
  - narrow dynamic range (recruitment)
  - unrealistic expectations
- types of hearing aids
  - BTE: behind-the-ear (with occlusive mould or open fit which allows natural sound to pass – for milder hearing losses)
  - ITE: in-the-ear, placed in concha
  - ITC: in-the-canal, placed entirely in ear canal
  - CIC: contained-in-canal, placed deeply in ear canal
  - bone conduction: bone-anchored hearing aid (BAHA): attached to the skull → BAHA: bone-anchored hearing aid: attached to skull (bone conduction)
  - CROS: contralateral routing of signals
- assistive listening devices
  - direct/indirect audio output
  - infrared, FM radio, or induction loop systems
  - telephone, television, or alerting devices
- cochlear implants
  - electrode is inserted into the cochlea to allow direct stimulation of the auditory nerve
  - for profound bilateral SNHL not rehabilitated with conventional hearing aids
  - established indication: post-lingually deafened adults, pre-and post-lingually deaf children



**Bone Anchored Hearing Aids (BAHA)**
BAHAs function based on bone conduction and are indicated primarily for patients with CHL, unilateral hearing loss, and mixed hearing loss who cannot wear conventional hearing aids. BAHAs consist of a titanium implant, an external abutment, and a sound processor. The sound processor transmits vibrations through the external abutment to the titanium implant and then directly to the cochlea



**Pre-lingual deafness**: deafness occurring before speech and language are acquired
**Post-lingual deafness**: deafness occurring after speech and language are acquired

# Vertigo

## Evaluation of the Dizzy Patient

- vertigo: illusion of rotational, linear, or tilting movement of self or environment
- vertigo is produced by peripheral (inner ear) or central (brainstem-cerebellum) stimulation
- it is important to distinguish vertigo from other potential causes of "dizziness" (see Figure 11, OT6)

**Table 5. Peripheral vs. Central Vertigo**

| Symptoms | Peripheral | Central |
|---|---|---|
| **Imbalance** | Moderate-severe | Mild-moderate |
| **Nausea and Vomiting** | Severe | Variable |
| **Auditory Symptoms** | Common | Rare |
| **Neurologic Symptoms** | Rare | Common |
| **Compensation** | Rapid | Slow |
| **Nystagmus** | Unidirectional<br>Horizontal or rotatory | Bidirectional<br>Horizontal or vertical |

**Table 6. Differential Diagnosis of Vertigo Based on History**

| Condition | Duration | Hearing Loss | Tinnitus | Aural Fullness | Other Features |
|---|---|---|---|---|---|
| **Benign Paroxysmal Positional Vertigo** (BPPV) | Seconds | – | – | – | |
| **Ménière's Disease** | Minutes to hours<br>Precedes attack | Uni/bilateral, fluctuating | + | Pressure/warmth | |
| **Labyrinthitis/Vestibular Neuronitis** | Hours to days | Unilateral | ±Whistling | – | May have recent AOM |
| **Acoustic Neuroma** | Chronic | Progressive | + | – | Ataxia<br>CN VII palsy |

**Table 7. Differential Diagnosis of Vertigo Based on Time Course**

| Time Course | Condition |
|---|---|
| Recurrent, lasting | BPPV |
| Single episode, lasting minutes to hours | Migraine, transient ischemia of the labyrinth or brainstem |
| Recurrent to hours | Ménière's |
| Prolonged | Vestibular neuritis, MS, brainstem/cerebellum infarct |
| Chronic | Acoustic neuroma |

# Benign Paroxysmal Positional Vertigo (BPPV)

BPPV is the most common cause of episodic vertigo; patients are often symptomatic when rolling over in bed or moving their head to a position of extreme posterior extension (such as looking up at a tall building or getting their hair washed at the hairdresser)

## Definition
- acute attacks of transient rotatory vertigo lasting seconds to minutes, initiated by certain head positions, accompanied by torsional (i.e. rotatory) nystagmus (geotropic = fast phase towards the floor)
- most common form of positional vertigo (50% of patients with peripheral vestibular dysfunction)

## Etiology
- due to canalithiasis (migration of free floating otoliths within the endolymph of the semicircular canal) or cupulolithiasis (otolith attached to the cupula of the semicircular canal)
  - can affect each of the 3 semicircular canals, although the posterior canal is affected in >90% of cases
  - causes: head injury, viral infection (URTI), degenerative disease, idiopathic
  - results in slightly different signals being received by the brain from the two balance organs, resulting in sensation of movement

## Diagnosis
- history (time course, provoking factors, associative symptoms)
- positive Dix-Hallpike maneuver (sensitivity 82%, specificity 71%)

**Signs of BPPV seen with Dix-Hallpike Maneuver**
- Latency of ~20 s
- Crescendo/decrescendo vertigo lasting 20 s
- Geotropic rotatory nystagmus (nystagmus MUST be present for a positive test)
- Reversal of nystagmus upon sitting up
- Fatigability with repeated stimulation

## Dix-Hallpike Positional Testing (see website for video and illustrations)
- the patient is rapidly moved from a sitting position to a supine position with the head hanging over the end of the table, turned to one side at 45°, and neck extended 20° holding the position for 20 s
- onset of vertigo and rotary nystagmus indicate a positive test for the dependent side
- other diagnostic testing is not indicated in posterior canal BPPV

## Treatment
- reassure patient that process resolves spontaneously
- particle repositioning maneuvers
  - Epley maneuver (performed by MD or by patient with the help of devices such as the DizzyFIX™)
  - Brandt-Daroff exercises (performed by patient)
- anti-emetics for N/V
- surgery for refractory cases
- drugs to suppress the vestibular system delay eventual recovery and are therefore not used

# Ménière's Disease (Endolymphatic Hydrops)

## Definition
- episodic attacks of tinnitus, hearing loss, aural fullness, and vertigo lasting min to hr

**Diagnostic Criteria for Ménière's Disease (must have all three)**
- Two spontaneous episodes of rotational vertigo ≥20 min
- Audiometric confirmation of SNHL (often low frequency)
- Tinnitus and/or aural fullness

## Proposed Etiology
- inadequate absorption of endolymph leads to endolymphatic hydrops (over accumulation) that distorts the membranous labyrinth

## Epidemiology
- peak incidence 40-60 yr
- bilateral in 35% of cases

### Clinical Features
- episodic vertigo, fluctuating low frequency SNHL, tinnitus, and aural fullness
- ± drop attacks (Tumarkin crisis), ± N/V
- vertigo disappears with time (min to h), but hearing loss remains
- early in the disease: fluctuating SNHL
- later stages: persistent tinnitus and progressive hearing loss
- attacks come in clusters and can be debilitating to the patient
- triggers: high salt intake, caffeine, stress, nicotine, and alcohol

### Treatment
- acute management may consist of bed rest, antiemetics, antivertiginous drugs (e.g. betahistine [Serc®], meclizine, dimenhydramine), and anticholinergics (e.g. scopolamine)
- long-term management may include
  - medical
    - low salt diet, diuretics (e.g. hydrochlorothiazide, triamterene, amiloride)
    - Serc® prophylactically to decrease intensity of attacks
    - intratympanic gentamicin to destroy vestibular end-organ, results in complete SNHL
    - intratympanic glucocorticoids (e.g. dexamethasone) may improve vertigo symptoms
  - surgical
    - selective vestibular neurectomy or labyrinthectomy
    - potential benefit for endolymphatic sac decompression or sacculotomy
    - must monitor opposite ear, as bilaterality occurs in 35% of cases

## Vestibular Neuronitis (Labyrinthitis)

### Definition
- acute onset of disabling vertigo often accompanied by N/V and imbalance without hearing loss that resolves over days, leaving a residual imbalance that lasts days to weeks
- vestibular neuronitis: inflammation of the vestibular portion of CN VIII
- labyrinthitis: inflammation of both vestibular and cochlear portions

### Etiology
- thought to be due to a viral infection (e.g. measles, mumps, herpes zoster) or post-viral syndrome
- only ~30% of cases have associated URTI symptoms
- labyrinthitis may occur as a complication of acute and chronic otitis media, bacterial meningitis, cholesteatoma, and temporal bone fractures

### Clinical Features
- acute phase
  - severe vertigo with N/V and imbalance lasting 1-5 d
  - irritative nystagmus (fast phase towards the offending ear)
  - ataxia: patient tends to veer towards affected side
  - tinnitus and hearing loss in labyrinthitis
- convalescent phase
  - imbalance and motion sickness lasting d-wk
  - spontaneous nystagmus away from affected side
  - gradual vestibular adaptation requires wk-mo

**Drop Attacks (Tumarkin's Otolithic Crisis)** are sudden falls occurring without warning and without loss of consciousness, where patient experiences feeling of being pushed down into the ground

### Treatment
- acute phase
  - bed rest, antivertiginous drugs
  - corticosteroids (methylprednisolone) ± antivirals
  - bacterial infection: treat with IV antibiotics, drainage of middle ear, ± mastoidectomy
- convalescent phase
  - progressive ambulation, especially in the elderly
  - vestibular exercises: involve eye and head movements, sitting, standing, and walking

Before proceeding with gentamicin treatment, perform a gadolinium-enhanced MRI to rule out CPA tumour as the cause of symptoms

## Acoustic Neuroma (Vestibular Schwannoma)

### Definition
- schwannoma of the vestibular portion of CN VIII

### Pathogenesis
- starts in the internal auditory canal and expands into CPA, compressing cerebellum and brainstem
- when associated with type 2 neurofibromatosis (NF2): bilateral acoustic neuromas, juvenile cataracts, meningiomas, and ependymomas

### Clinical Features
- usually presents with unilateral SNHL (chronic) or tinnitus
- dizziness and unsteadiness may be present, but true vertigo is rare as tumour growth occurs slowly, and thus compensation occurs

Acoustic neuroma is the most common intracranial tumour causing SNHL and the most common CPA tumour

In the elderly, unilateral tinnitus or SNHL is acoustic neuroma until proven otherwise

- facial nerve palsy and trigeminal (V1) sensory deficit (corneal reflex) are late complications
- risk factors: exposure to loud noise, childhood exposure to low-dose radiation, history of parathyroid adenoma

### Diagnosis
- MRI with gadolinium contrast (gold standard)
- audiogram (to assess SNHL)
- poor speech discrimination relative to the hearing loss
- stapedial reflex absent or significant reflex decay
- ABR: increase in latency of the 5th wave
- vestibular tests: normal or asymmetric caloric weakness (an early sign)

### Treatment
- expectant management if tumour is very small, or in elderly
- definitive management is surgical excision
- other options: gamma knife, radiation

# Tinnitus

### Definition
- an auditory perception in the absence of an acoustic stimuli, likely related to loss of input to neurons in central auditory pathways and resulting in abnormal firing

### History
- subjective vs. objective (see Figure 14, OT7)
- continuous vs. pulsatile (vascular in origin)
- unilateral vs. bilateral
- associated symptoms: hearing loss, vertigo, aural fullness, otalgia, otorrhea

### Investigations
- audiology
- if unilateral
  - ABR, gadolinium-enhanced MRI to exclude a retrocochlear lesion
  - CT to diagnose glomus tympanicum (rare)
  - MRI or angiogram to diagnose arteriovenous malformation
- if suspect metabolic abnormality: lipid profile, TSH, zinc levels

### Treatment
- if a cause is found, treat the cause (e.g. drainage of middle ear effusion, embolization or excision of arteriovenous malformation)
- with no treatable cause: 50% will improve, 25% worsen, 25% remain the same
- avoid loud noise, ototoxic meds, caffeine, smoking
- tinnitus clinics
- identify situations where tinnitus is most bothersome (e.g. quiet times), mask tinnitus with soft music or "white noise"
- hearing aid if coexistent hearing loss
- tinnitus instrument: combines hearing aid with white noise masker
- trial of tocainamide

Cerumen impaction is the most common cause of CHL for those aged 15-50 yr

# Diseases of the External Ear

## Cerumen Impaction

### Etiology
- ear wax: a mixture of secretions from ceruminous and pilosebaceous glands, squames of epithelium, dust, and debris

### Risk Factors
- hairy or narrow ear canals, in-the-ear hearing aids, cotton swab usage, osteomata

### Clinical Features
- hearing loss (conductive)
- ± tinnitus, vertigo, otalgia, aural fullness

### Treatment
- water or ceruminolytic drops (bicarbonate solution, olive oil, glycerine, Cerumenol®, Cerumenex®)
- manual debridement (by MD)

**Syringing**

**Indications**
- Totally occlusive cerumen with pain, decreased hearing, or tinnitus

**Contraindications**
- Active infection
- Previous ear surgery
- Only hearing ear
- TM perforation

**Complications**
- Otitis externa
- TM perforation
- Trauma
- Pain
- Vertigo
- Tinnitus
- Otitis media

**Method**
- Establish that TM is intact
- Gently pull the pinna superiorly and posteriorly
- Using lukewarm water, aim the syringe nozzle upwards and posteriorly to irrigate the ear canal

# Exostoses

### Definition
- bony protuberances in the external auditory canal composed of lamellar bone

### Etiology
- possible association with swimming in cold water

### Clinical Features
- usually an incidental finding
- if large, they can cause cerumen impaction or otitis externa

### Treatment
- no treatment required unless symptomatic

# Otitis Externa

### Definition
- inflammation of external auditory canal or auricle

### Etiology
- bacterial (90% of OE): *Pseudomonas aeruginosa, Pseudomonas vulgaris, E. coli, S. aureus*
- fungal: *Candida albicans, Aspergillus niger*

### Risk Factors
- associated with swimming ("swimmer's ear")
- mechanical cleaning (Q-tips®), skin dermatitis, aggressive scratching
- devices that occlude the ear canal: hearing aids, headphones, etc.
- allergic contact dermatitis, dermatologic conditions (psoriasis, atopic dermatitis)

### Clinical Features
- acute
  - pain aggravated by movement of auricle (traction of pinna or pressure over tragus)
  - otorrhea (sticky, yellow purulent discharge)
  - CHL ± aural fullness secondary to obstruction of external canal by swelling and purulent debris
  - posterior auricular lymphadenopathy
  - complicated OE exists if the pinna and/or the periauricular soft tissues are erythematous and swollen
- chronic
  - pruritus of external ear ± excoriation of ear canal
  - atrophic and scaly epidermal lining, ± otorrhea, ± hearing loss
  - wide meatus but no pain with movement of auricle
  - TM appears normal



Pulling on the pinna is extremely painful in OE, but is usually well tolerated in otitis media

### Treatment
- clean ear under magnification with irrigation, suction, dry swabbing, and C&S
- bacterial etiology
  - antipseudomonal otic drops (e.g. ciprofloxacin) or a combination of antibiotic and steroid (e.g. Cipro HC®)
  - do not use aminoglycoside if the TM is perforated, because of the risk of ototoxicity
  - introduction of fine gauze wick (pope wick) if external canal edematous
  - ± 3% acetic acid solution to acidify ear canal (low pH is bacteriostatic)
  - systemic antibiotics if either cervical lymphadenopathy or cellulitis is present
- fungal etiology
  - repeated debridement and topical antifungals (gentian violet, Mycostatin® powder, boric acid, Locacorten®, Vioform® drops)
- ± analgesics
- chronic otitis externa (pruritus without obvious infection) → corticosteroid alone (e.g. diprosalic acid)

# Malignant (Necrotizing) Otitis Externa (Skull Base Osteomyelitis)

### Definition
- osteomyelitis of the temporal bone

### Epidemiology
- occurs in elderly diabetics and immunocompromised patients

### Etiology
- rare complication of otitis externa
- *Pseudomonas* infection in 99% of cases

### Clinical Features
- otalgia and purulent otorrhea that is refractory to medical therapy
- granulation tissue on the floor of the auditory canal

### Complications
- cranial nerve palsy (most commonly CN VII>CN X>CN XI)
- systemic infection, death

### Management
- imaging: high resolution temporal bone CT scan, gadolinium-enhanced MRI, technetium scan
- requires hospital admission, debridement, IV antibiotics, hyperbaric $O_2$
- may require OR for debridement of necrotic tissue/bone

**Gallium and Technetium Scans**
Gallium scans are used to show sites of active infection. Gallium is taken up by polymorphonuclear leukocytes, and therefore only lights up when active infection is present. It will not show the extent of osteomyelitis. Technetium scans provide information about osteoblastic activity and, as a result, are used to demonstrate sites of osteomyelitis. Technetium scans help with diagnosis, whereas gallium scans are useful in follow-up

# Diseases of the Middle Ear

## Acute Otitis Media and Otitis Media with Effusion

- see *Pediatric Otolaryngology*, OT38

## Chronic Otitis Media

### Definition
- an ear with TM perforation in the setting of recurrent or chronic ear infections

### Benign
- dry TM perforation without active infection

### Chronic Serous Otitis Media
- continuous serous drainage (straw-coloured)

### Chronic Suppurative Otitis Media
- persistent purulent drainage through a perforated TM

## Cholesteatoma

### Definition
- a cyst composed of keratinized desquamated epithelial cells occurring in the middle ear, mastoid, and temporal bone
- two types: congenital and acquired

### Congenital
- presents as a "small white pearl" behind an intact TM (anterior and medial to the malleus) or as CHL
- believed to be due to aberrant migration of external canal ectoderm during development
- not associated with otitis media/Eustachian tube dysfunction

### Acquired (more common)
- primary cholesteatoma
  - frequently associated with retraction pockets in the pars flaccida (may lead to attic cholesteatomas, which are difficult to visualize)
  - often has crusting or desquamated debris on lateral surface
- secondary cholesteatoma
  - pearly mass evident behind TM, frequently associated with marginal perforation
  - may appear as skin that have replaced the mucosa of the middle ear
- the associated chronic inflammatory process causes progressive destruction of surrounding bony structures

**Mechanisms of Cholesteatoma Formation**
- Epithelial migration through TM perforation (2° acquired)
- Invagination of TM (1° acquired)
- Metaplasia of middle ear epithelium or basal cell hyperplasia (congenital)

### Clinical Features
- history of otitis media (especially if unilateral), ventilation tubes, ear surgery
- symptoms
  - progressive hearing loss (predominantly conductive, although may get SNHL in late stage)
  - otalgia, aural fullness, fever
- signs
  - retraction pocket in TM, may contain keratin debris
  - TM perforation
  - granulation tissue, polyp visible on otoscopy
  - malodourous, unilateral otorrhea

### Complications

**Table 8. Complications of Cholesteatoma**

| Local | Intracranial |
|---|---|
| Ossicular erosion: CHL | Meningitis |
| Inner ear erosion: SNHL, dizziness, and/or labyrinthitis | Sigmoid sinus thrombosis |
| Temporal bone infection: mastoiditis, petrositis | Intracranial abscess (subdural, epidural, cerebellar) |
| Facial paralysis | |

### Investigations
- audiogram and CT scan

### Treatment
- there is no conservative therapy for cholesteatoma
- surgical: mastoidectomy ± tympanoplasty ± ossicular reconstruction

## Mastoiditis

### Definition
- infection (usually subperiosteal) of mastoid air cells, most commonly seen approximately two wk after onset of untreated or inadequately treated AOM (suppurative)
- more common in children than adults

### Etiology
- acute mastoiditis is caused by the same organisms as AOM: *S. pneumoniae, H. influenzae, M. catarrhalis, S. pyogenes, S. aureus, P. aeruginosa,* etc.

### Clinical Features
- otorrhea
- tenderness to pressure over the mastoid
- retroauricular swelling with protruding ear
- fever, hearing loss, ± TM perforation (late)
- CT radiologic findings: opacification of mastoid air cells by fluid and interruption of normal trabeculations of cells (coalescence)

**Classic Triad**
- Otorrhea
- Tenderness to pressure over the mastoid
- Retroauricular swelling with protruding ear

### Treatment
- IV antibiotics with myringotomy and ventilation tubes – usually all that is required in acute cases
- cortical mastoidectomy
  - debridement of infected tissue allowing aeration and drainage
- indications for surgery
  - failure of medical treatment after 48 h
  - symptoms of intracranial complications
  - aural discharge persisting for 4 wk and resistant to antibiotics

Complications of AOM are rare due to rapid and effective treatment of AOM with antibiotics

## Otosclerosis

### Definition
- fusion of stapes footplate to oval window so that it cannot vibrate

### Etiology
- autosomal dominant, variable penetrance approximately 40%
- F>M, progresses during pregnancy (hormone responsive)

Otosclerosis is the 2nd most common cause of CHL in 15-50 yr old (after cerumen impaction)

### Clinical Features
- progressive CHL first noticed in teens and 20s (may progress to SNHL if cochlea involved)
- ± pulsatile tinnitus
- TM normal ± pink blush (Schwartz's sign) associated with the neovascularization of otosclerotic bone
- characteristic dip at 2000 Hz (Carhart's notch) on audiogram (see Figure 16C, OT10)

### Treatment
- monitor with serial audiograms if coping with loss
- hearing aid (air conduction, bone conduction, BAHA)
- AC and BC instead of air conduction, bone conduction
- stapedectomy or stapedotomy (with laser or drill) with prosthesis is definitive treatment

# Diseases of the Inner Ear

## Congenital Sensorineural Hearing Loss

### Hereditary Defects
- non-syndrome associated (70%)
  - often idiopathic, autosomal recessive
  - connexin 26 (GJB2) most common
- syndrome associated (30%)
  - Waardenburg: white forelock, heterochromia iridis (each eye different colour), wide nasal bridge, and increased distance between medial canthi
  - Pendred: deafness associated with thyroid gland disorders, SLC26A4 gene, enlarged vestibular aqueducts
  - Treacher-Collins: first and second branchial cleft anomalies
  - Alport: hereditary nephritis

### Prenatal Infections
- TORCH: toxoplasmosis, others (e.g. HIV, syphilis), rubella, CMV, HSV
- Zika

### Perinatal
- Rh incompatibility
- anoxia
- hyperbilirubinemia
- birth trauma (hemorrhage into inner ear)

### Postnatal
- meningitis, mumps, measles

### High Risk Factors (for hearing loss in newborns)
- low birth weight/prematurity
- perinatal anoxia (low APGARs)
- kernicterus: bilirubin >25 mg/dL
- craniofacial abnormality
- family history of deafness in childhood
- 1st trimester illness: TORCH infections
- neonatal sepsis
- ototoxic drugs
- perinatal infection, including post-natal meningitis
- consanguinity
- 50-75% of newborns with SNHL have at least one of the above risk factors and 90% of these have spent time in the NICU

### Treatment
- presence of any risk factor: ABR study performed before leaving NICU and at 3 mo adjusted age
- early rehabilitation improves speech and school performance

## Presbycusis



Presbycusis is the most common cause of SNHL

### Definition
- SNHL associated with aging (starting in 5th and 6th decades)

### Etiology
- hair cell degeneration
- age related degeneration of basilar membrane, possibly genetic etiology
- cochlear neuron damage
- ischemia of inner ear

### Clinical Features
- progressive, bilateral hearing loss initially at high frequencies, then middle frequencies
- loss of discrimination of speech, especially with background noise present – patients describe people as mumbling
- recruitment phenomenon: inability to tolerate loud sounds
- tinnitus

### Treatment
- hearing aid if patient has difficulty functioning, hearing loss >30-35 dB, and good speech discrimination
- ± lip reading, auditory training, auditory aids (doorbell and phone lights)

# Sudden Sensorineural Hearing Loss

### Clinical Features
- presents as a sudden onset of significant SNHL (usually unilateral) ± tinnitus, aural fullness
- usually idiopathic; rule out other causes
  - autoimmune causes (e.g. ESR, rheumatoid factor, ANA)
  - MRI to rule out tumour and/or CT to rule out ischemic/hemorrhagic stroke if associated with any other focal neurological signs (e.g. vertigo, ataxia, abnormality of CN V or VII, weakness)

### Treatment
- intratympanic or oral corticosteroids within 3 d of onset: prednisone 1 mg/kg/d for 10-14 d

### Prognosis
- depends on degree of hearing loss
- 70% resolve within 10-14 d
- 20% experience partial resolution
- 10% experience permanent hearing loss



Sudden SNHL may easily be confused with ischemic brain events. It is important to keep a high index of suspicion especially with elderly patients presenting with sudden SNHL as well as vertigo



**Steroids for Treatment of Sudden Sensorineural Hearing Loss: A Meta-Analysis of RCTs**
Laryngoscope 2015;125(1):209-17
**Summary**: A meta-analysis of randomized controlled trials does not support the use of steroids over placebo in this condition, a finding consistent with previous analyses.

# Autoimmune Inner Ear Disease

### Etiology
- idiopathic
- may be associated with systemic autoimmune diseases (e.g. rheumatoid arthritis, SLE), vasculitides (e.g. GPA, polyarteritis nodosa), and allergies

### Epidemiology
- most common between ages 20-50

### Clinical Features
- rapidly progressive or fluctuating bilateral SNHL
- ± tinnitus, aural fullness, vestibular symptoms (e.g. ataxia, disequilibrium, vertigo)

### Investigations
- autoimmune workup: CBC, ESR, ANA, rheumatoid factor

### Treatment
- high-dose corticosteroids: treat early for at least 30 d
- consider cytotoxic medication for steroid non-responders

# Drug Ototoxicity

### Aminoglycosides
- streptomycin and gentamicin (vestibulotoxic), kanamycin, and tobramycin (cochleotoxic)
- toxic to hair cells by any route: oral, IV, and topical (if the TM is perforated)
- destroys sensory hair cells: outer first, inner second (therefore, otoacoustic emissions are lost first)
- high frequency hearing loss develops earliest
- ototoxicity occurs d-wk post-treatment
- must monitor with peak and trough levels when prescribed, especially if patient has neutropenia and/or history of ear or renal problems
- q24h dosing recommended (with amount determined by creatinine clearance)
- aminoglycoside toxicity displays saturable kinetics, therefore, once daily dosing presents less risk than divided daily doses
- duration of treatment is the most important predictor of ototoxicity
  - treatment: immediately stop aminoglycosides

### Salicylates
- hearing loss with tinnitus, reversible if discontinued

### Antimalarials (Quinines)
- hearing loss with tinnitus
- reversible if discontinued, but can lead to permanent loss

### Others
- many antineoplastic agents are ototoxic (weigh risks vs. benefits)
- loop diuretics

# Noise-Induced Sensorineural Hearing Loss

## Pathogenesis
- 85-90 dB over months or years or single sound impulses >135 dB can cause cochlear damage
- bilateral SNHL initially and most prominently at 4000 Hz (resonant frequency of the temporal bone), known as "boilermaker's notch" on audiogram, extends to higher and lower frequencies with time (see Figure 16D, OT10)
- speech reception not altered until hearing loss >30 dB at speech frequency, therefore considerable damage may occur before patient complains of hearing loss
- difficulty with speech discrimination, especially in situations with competing noise

## Phases of Hearing Loss
- dependent on: intensity of sound and duration of exposure
  - temporary threshold shift
    - when exposed to loud sound, decreased sensitivity or increased threshold for sound
    - may have associated aural fullness and tinnitus
    - with removal of noise, hearing returns to normal
  - permanent threshold shift
- hearing does not return to previous state

## Treatment
- hearing aid
- prevention
  - ear protectors: muffs, plugs
  - limit exposure to noise with frequent rest periods
  - regular audiologic follow-up

# Temporal Bone Fractures

**Table 9. Features of Temporal Bone Fractures**

| | Transverse (1) | Longitudinal (2) |
|---|---|---|
| **Extension** | Into bony labyrinth and internal auditory meatus | Into middle ear |
| **Incidence** | 10-20% | 70-90% |
| **Etiology** | Frontal/occipital trauma | Lateral skull trauma |
| **CN Pathology** | CN VII palsy (50%) | CN VII palsy (10-20%) |
| **Hearing Loss** | SNHL due to direct cochlear injury | CHL 2° to ossicular injury |
| **Vestibular Symptoms** | Sudden onset vestibular symptoms due to direct semicircular canal injury (vertigo, spontaneous nystagmus) | Rare |
| **Other Features** | Intact external auditory meatus, TM ± hemotympanum<br>Spontaneous nystagmus<br>CSF leak in Eustachian tube to nasopharynx<br>± rhinorrhea (risk of meningitis) | Torn TM or hemotympanum<br>Bleeding from external auditory canal<br>Step formation in external auditory canal<br>CSF otorrhea<br>Battle's sign = mastoid ecchymoses<br>Raccoon eyes = periorbital ecchymoses |

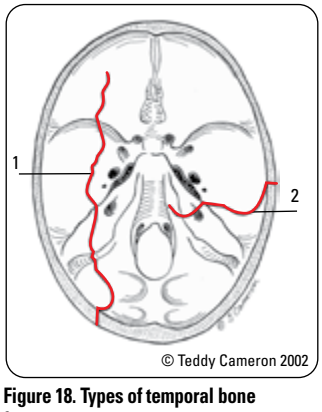



**Figure 18. Types of temporal bone fractures**

- characterized as longitudinal or transverse relative to the long axis of the petrous temporal bone
- temporal bone fractures are rarely purely transverse or longitudinal (often a mixed picture)

## Diagnosis
- otoscopy
- do not syringe or manipulate external auditory meatus due to risk of inducing meningitis via TM perforation
- CT head
- audiology, facial nerve tests (for transverse fractures), Schirmer's test (of lacrimation), stapedial reflexes if CN VII palsy
- if suspecting CSF leak: look for halo sign, send fluid for β-2 transferrin or β trace protein (prostaglandin D synthase)

## Treatment
- ABCs
- medical: expectant, prevent otogenic meningitis
- surgical: explore temporal bone; indications:
  - CN VII palsy (immediate and complete)
  - gunshot wound
  - depressed fracture of external auditory meatus
  - early meningitis (mastoidectomy)
  - bleeding intracranially from sinus
  - CSF otorrhea (may resolve spontaneously)

Hemotympanum can be indicative of temporal bone trauma

**Signs of Basilar Skull Fracture**
- Battle's Sign
- Racoon Eyes
- CSF Rhinorrhea/Otorrhea
- Cranial Nerve Involvement:
  facial palsy → CN VII,
  nystagmus → CN VI,
  facial numbness → CN V

### Complications
- AOM ± labyrinthitis ± mastoiditis
- meningitis/epidural abscess/brain abscess
- post-traumatic cholesteatoma

# Facial Nerve (CN VII) Paralysis

### Peripheral Facial Paralysis (PFP)
- mononeuropathy of the facial nerve where there is weakening in the facial muscles, which alters facial symmetry and functions
- can have a detectable cause (secondary facial nerve palsy) or may be idiopathic (primary)

### Etiology
- supranuclear and nuclear (MS, poliomyelitis, cerebral tumours)
- infranuclear

### Treatment
- treat according to etiology, plus provide corneal protection with artificial tears, nocturnal lid taping, tarsorrhaphy, gold weighting of upper lid
- facial paralysis that does not resolve with time or with medical treatment will often be referred for possible reanimation techniques to restore function
  - common reanimation techniques include:
    - direct facial nerve anastomosis
    - interpositional grafts
    - anastomosis to other motor nerves
    - muscle transpositions

**Table 10. Differential Diagnosis of Peripheral Facial Paralysis (PFP)**

| Etiology | Incidence | Findings | Investigations | Treatment, Follow-up, and Prognosis (Px) |
|---|---|---|---|---|
| **Bell's Palsy**<br>Idiopathic, (HSV) infection of the facial nerve<br>Diagnosis of exclusion | 80-90% of PFP<br>**Risk Factors:**<br>DM<br>Pregnancy<br>Viral prodrome (50%) | **Hx**<br>Acute onset<br>Numbness of ear<br>Schirmer's test<br>Recurrence (12%)<br>+ FHx (14%)<br>Hyperacusis (30%)<br>**P/E**<br>Paralysis or paresis of all muscle groups on one side of the face<br>Absence of signs of CNS disease<br>Absence of signs of ear or CPA diseases | Stapedial reflex absent<br>Audiology normal (or baseline)<br>EMG – best measure for prognosis<br>Topognostic testing<br>MRI with gadolinium – enhancement of CN VII and VIII<br>High resolution CT | **Rx**<br>Protect the eye to prevent exposure keratitis with patching or tarsorraphy<br>Systemic steroids may lessen degeneration and hasten recovery<br>Consider antiviral (acyclovir)<br>**F/U**<br>Spontaneous remission should begin within 3 wk of onset<br>Delayed (3-6 mo) recovery portends at least some functional loss<br>**Px**<br>electroneuronography (ENoG) testing between day 3-14 of onset:<br><90% degeneration = high likelihood of recovery<br>>90% + no voluntary EMG motor unit potentials = surgical decompression<br>Poorer if hyperacusis, >60 yr, DM, HTN, severe pain |
| **Ramsay Hunt Syndrome** (Herpes Zoster Oticus)<br>Varicella zoster infection of CN VII/VIII | 4.5-9% of PFP<br>**Risk Factors:**<br>>60 yr<br>Impaired immunity<br>Cancer<br>Radiotherapy<br>Chemotherapy | **Hx**<br>Hyperacusis<br>SNHL<br>Severe pain of pinna, mouth, or face<br>**P/E**<br>Vesicles on pinna, external canal (errupt 3-7 d after onset of pain)<br>Associated herpes zoster ophthalmicus (uveitis, keratoconjunctivitis, optic neuritis, or glaucoma) | Stapedial reflex absent<br>Audiology – SNHL<br>Viral ELISA studies to confirm<br>MRI with gadolinium (86% of facial nerves enhance) | **Rx**<br>Avoid touching lesions to prevent spread of infection<br>Systemic steroids can relieve pain, vertigo, avoid postherpetic neuralgia<br>Acyclovir may lessen pain, aid healing of vesicles<br>**F/U:** 2-4 wk<br>**Px**<br>Poorer prognosis than Bell's palsy; 22% recover completely, 66% incomplete paralysis, 10% complete paralysis |
| **TEMPORAL BONE FRACTURE** *rarely a patient has a single type of fracture | | | | |
| **Longitudinal** (90%) | 20% have PFP | **Hx**<br>Blow to side of head<br>**P/E**<br>Trauma to side of head<br>Neuro findings consistent with epidural/subdural bleed | Skull X-rays<br>CT head | **Px**<br>Injury usually due to stretch or impingement; may recover with time |
| **Transverse** (10%) | 40% have PFP | **Hx**<br>Blow to frontal or occipital area<br>**P/E**<br>Trauma to front or back of head | Skull X-rays<br>CT head | **Px**<br>Nerve transection more likely |
| **Iatrogenic** | | Variable (depending on level of injury) | Wait for lidocaine to wear off<br>EMG | **Rx**<br>Exploration if complete nerve paralysis<br>No exploration if any movement present |

Source: Paul Warrick, MD

# Rhinitis

## Definition
- inflammation of the lining (mucosa) of the nasal cavity

**Table 11. Classification of Rhinitis**

| Inflammatory | Non-Inflammatory |
|---|---|
| Perennial non-allergic<br>Asthma, ASA sensitivity<br>Allergic<br>Seasonal<br>Perennial<br>Atrophic<br>Primary: *Klebsiella ozena* (especially in elderly)<br>Acquired: post-surgery if too much mucosa or turbinate has been resected<br>Infectious<br>Viral: e.g. rhinovirus, influenza, parainfluenza, etc.<br>Bacterial: e.g. *S. aureus*<br>Fungal<br>Granulomatous: TB, syphilis, leprosy<br>Non-infectious<br>Sarcoidosis<br>GPA<br>Irritant<br>Dust<br>Chemicals<br>Pollution | Rhinitis medicamentosa<br>Topical decongestants<br>Hormonal<br>Pregnancy<br>Estrogens<br>Thyroid<br>Idiopathic vasomotor |



**Rhinitis medicamentosa:** rebound congestion due to the overuse of intranasal vasoconstrictors; for prevention, use of these medications for only 5-7 d is recommended

**Table 12. Nasal Discharge: Character and Associated Conditions**

| Character | Associated Conditions |
|---|---|
| **Watery/Mucoid** | Allergic, viral, vasomotor, CSF leak (halo sign) |
| **Mucopurulent** | Bacterial, foreign body |
| **Serosanguinous** | Neoplasia |
| **Bloody** | Trauma, neoplasia, bleeding disorder, HTN/vascular disease |

# Allergic Rhinitis (i.e. Hay Fever)

## Definition
- rhinitis characterized by an IgE-mediated hypersensitivity to foreign allergens
- acute-and-seasonal or chronic-and-perennial
- perennial allergic rhinitis often confused with recurrent colds



Congestion reduces nasal airflow and allows the nose to repair itself (i.e. washes away the irritants). Treatment should focus on the initial insult rather than target this defense mechanism

## Etiology
- when allergens contact the respiratory mucosa, specific IgE antibody is produced in susceptible hosts
- concentration of allergen in the ambient air correlates directly with the rhinitis symptoms

## Epidemiology
- age at onset usually <20 yr
- more common in those with a personal or family history of allergies/atopy

## Clinical Features
- nasal: obstruction with pruritus, sneezing
- clear rhinorrhea (containing increased eosinophils)
- itching of eyes with tearing
- frontal headache and pressure
- mucosa: swollen, pale, "boggy"
- seasonal (summer, spring, early autumn)
  - pollens from trees
  - lasts several wk, disappears, and recurs the following year at same time
- perennial
  - inhaled: house dust, wool, feathers, foods, tobacco, hair, mould
  - ingested: wheat, eggs, milk, nuts
  - occurs intermittently for years with no pattern or may be constantly present

### Complications
- chronic sinusitis/polyps
- serous otitis media

### Diagnosis
- history
- direct exam
- allergy testing

### Treatment
- education: identification and avoidance of allergen
- nasal irrigation with saline
- antihistamines (e.g. diphenhydramine, fexofenadine)
- oral decongestants (e.g. pseudoephedrine, phenylpropanolamine)
- topical decongestant (may lead to rhinitis medicamentosa)
- other topicals: steroids (fluticasone), disodium cromoglycate, antihistamines, ipratropium bromide
- oral steroids if severe
- desensitization by allergen immunotherapy

## Vasomotor Rhinitis

### Definition
- neurovascular disorder of nasal parasympathetic system (vidian nerve) affecting mucosal blood vessels
- nonspecific reflex hypersensitivity of nasal mucosa

### Etiology
- temperature change
- alcohol, dust, smoke
- stress, anxiety, neurosis
- endocrine: hypothyroidism, pregnancy, menopause
- parasympathomimetic drugs
- beware of rhinitis medicamentosa: reactive vasodilation due to prolonged use (>5 d) of nasal drops and sprays (Dristan®, Otrivin®)

### Clinical Features
- chronic intermittent nasal obstruction, varies from side to side
- rhinorrhea: thin, watery
- mucosa and turbinates: swollen
- nasal allergy must be ruled out

### Treatment
- elimination of irritant factors
- parasympathetic blocker (Atrovent® nasal spray)
- steroids (e.g. beclomethasone, fluticasone)
- surgery (often of limited lasting benefit): electrocautery, cryosurgery, laser treatment, or removal of inferior or middle turbinates
- vidian neurectomy (rarely done)
- symptomatic relief with exercise (increased sympathetic tone)

## Rhinosinusitis

### Definition
- inflammation of the mucosal lining of the sinuses and nasal passages

### Pathogenesis of Rhinosinusitis
- ostial obstruction or dysfunctional cilia permit stagnant mucous and, consequently, infection
- all sinuses drain to a common prechamber under the middle meatus called the osteomeatal complex

### Classification
- acute: <4 wk
- subacute: 4-8 wk
- chronic: >8-12 wk

**Table 13. Etiologies of Rhinosinusitis**

| | | |
|---|---|---|
| **Ostial Obstruction** | Inflammation | URTI<br>Allergy |
| | Mechanical | Septal deviation<br>Turbinate hypertrophy<br>Polyps<br>Tumours<br>Adenoid hypertrophy<br>Foreign body<br>Congenital abnormalities (e.g. cleft palate) |
| | Immune | PA<br>Lymphoma, leukemia<br>Immunosuppressed patients (e.g. neutropenics, diabetics, HIV) |
| **Systemic** | | Cystic fibrosis<br>Immotile cilia (e.g. Kartagener's syndrome) |
| **Direct Extension** | Dental | Infection |
| | Trauma | Facial fractures |

# Acute Bacterial Rhinosinusitis

## Definition

- bacterial infection of the paranasal sinuses and nasal passages lasting >7 d
- clinical diagnosis requiring ≥2 major symptoms, and at least one of the symptoms is either nasal obstruction or purulent/discoloured nasal discharge

| | **Major Symptoms (at least 2 of PODS, 1 must be O or D)** | **Minor Symptoms** |
|---|---|---|
| **P** | Facial **P**ain/**P**ressure/fullness | Headache |
| **O** | Nasal **O**bstruction | Halitosis |
| **D** | Purulent/discoloured nasal **D**ischarge | Fatigue |
| **S** | Hyposmia/anosmia (**S**mell) | Dental pain |
| | | Cough |
| | | Ear pain/fullness |

## Etiology

- bacteria: *S. pneumoniae* (35%), *H. influenzae* (35%), *M. catarrhalis, S. aureus*, anaerobes (dental)
- children are more prone to a bacterial etiology, but viral is still more common
- maxillary sinus most commonly affected
- must rule out fungal causes (mucormycosis) in immunocompromised hosts (especially if painless black or pale mucosa on examination)

## Clinical Features

- sudden onset of:
  - nasal blockage/congestion and/or purulent nasal discharge/posterior nasal drip
  - ± facial pain or pressure, hyposmia, sore throat
- persistent/worsening symptoms >5-7 d or presence of purulence for 3-4 d with high fever
- speculum exam: erythematous mucosa, mucopurulent discharge, pus originating from the middle meatus
- predisposing factors: viral URTI, allergy, dental disease, anatomical defects
- differentiate from acute viral rhinosinusitis (course: <10 d, peaks by day 3)

## Diagnosis

- along with clinical criteria, can confirm radiographically and/or endoscopically using antral puncture for bacterial cultures

## Management

- depends on symptom severity (i.e. intensity/duration of symptoms, impact on quality of life)
- mild-moderate: INCS
  - if no response within 72 h, add antibiotics
- severe: INCS + antibiotics
- antibiotics
  - 1st line: amoxicillin x 10 d (TMP-SMX or macrolide if penicillin allergy)
- if no response to 1st line antibiotics within 72 h, switch to 2nd line
  - 2nd line: fluoroquinolones or amoxicillin-clavulanic acid
- adjuvant therapy (saline or hypochlorous acid (pediatric sinusitis) irrigation, analgesics, oral/topical decongestant) may provide symptomatic relief
- CT indicated only if complications are suspected



**Acute Rhinosinusitis Complications**
Consider hospitalization if any of the following are suspected
**Orbital (Chandler's classification)**
- Preseptal cellulitis
- Postseptal cellulitis
- Subperiosteal abscess
- Orbital abscess
- Cavernous sinus thrombosis

**Intracranial**
- Meningitis
- Abscess

**Bony**
- Subperiosteal frontal bone abscess ("Pott's Puffy tumour")
- Osteomyelitis

**Neurologic**
- Superior orbital fissure syndrome (CN III/IV/VI palsy, immobile globe, dilated pupils, ptosis, V1 hypoesthesia)
- Orbital apex syndrome (as above, plus neuritis, papilledema, decreased visual acuity)



**Systemic Corticosteroid Therapy for Acute Sinusitis**
JAMA 2015 Mar;313(12):1258-9
**Clinical Question**: Are oral or parenteral corticosteroids associated with improved clinical outcomes in patients with acute sinusitis compared with placebo or NSAIDs?
**Conclusion**: Oral corticosteroids combined with antibiotics may be associated with modest benefit for short-term relief of symptoms in adults with severe symptoms of acute sinusitis compared with antibiotics alone. Oral corticosteroids as monotherapy are not associated with improved clinical outcomes in adults with clinically diagnosed acute sinusitis.

# Chronic Rhinosinusitis

### Definition
- inflammation of the mucosa of paranasal sinuses and nasal passages >8-12 wk
- diagnosis requires ≥2 major symptoms for >8-12 wk and ≥1 objective finding of inflammation of the paranasal sinuses (CT/endoscopy)

### Etiology
- unclear etiology but the following may contribute or predispose
  - inadequate treatment of acute rhinosinusitis
  - bacterial colonization/biofilms
- *S. aureus, Enterobacteriaceae, Pseudomonas, S. pneumoniae, H. influenzae*, group A β-hemolytic *Streptococcus*
  - fungal infection (e.g. *Aspergillus, Zygomycetes, Candida*)
  - anatomic abnormality (e.g. lost ostia patency, deviated septum – predisposing factors)
  - allergy/allergic rhinitis
  - ciliary disorder (e.g. cystic fibrosis, Kartagener syndrome)
  - chronic inflammatory disorder (e.g. GPA)
  - untreated dental disease

**Allergic Fungal Rhinosinusitis**
- A chronic sinusitis affecting mostly young, immunocompetent, atopic individuals
- Treatment options include FESS ± intranasal topical steroids, antifungals, and immunotherapy

### Clinical Features (similar to acute, but less severe) - at least 2 of CPODS for >8-12 wk
- facial **C**ongestion/fullness
- facial **P**ain/**P**ressure
- chronic nasal **O**bstruction
- purulent anterior/posterior nasal **D**ischarge
- hyposmia/anosmia (**S**mell)
- others: halitosis, chronic cough, maxillary dental pain

### Management
- identify and address contributing or predisposing factors
- obtain CT or perform endoscopy
- if polyps present: INCS, oral steroids ± antibiotics (if signs of infection), refer to otolaryngologist/H&N surgeon
- if polyps absent: INCS, antibiotics, saline irrigation, oral steroids (severe cases)
- antibiotics for 3-6 wk
  - amoxillin-clavulanic acid, fluoroquinolone (moxifloxacin), macrolide (clarithromycin), clindamycin (metronidazole)
- surgery if medical therapy fails or fungal sinusitis: FESS, balloon sinoplasty

**FESS = Functional Endoscopic Sinus Surgery**
Opening of the entire osteomeatal complex in order to facilitate drainage while sparing the sinus mucosa

### Complications
- same as acute sinusitis, mucocele

# Epistaxis

### Blood Supply to the Nasal Septum (see Figure 4, OT3)
1. Superior posterior septum
   - internal carotid → ophthalmic → anterior/posterior ethmoidal
2. Posterior septum
   - external carotid → internal maxillary → sphenopalatine → nasopalatine
3. Lower anterior septum
   - external carotid → facial artery → superior labial artery → nasal branch
   - external carotid → internal maxillary → descending palatine → greater palatine
- these arteries all anastomose to form Kiesselbach's plexus, located at Little's area (anterior-inferior portion of the cartilaginous septum)
- bleeding from above middle turbinate is internal carotid, from below is external carotid

90% of nose bleeds occur in Little's area

**Table 14. Etiology of Epistaxis**

| Type | Causes | |
|---|---|---|
| **Local** | Trauma (most common)<br>Fractures: facial, nasal<br>Self-induced: digital, foreign body | Tumours<br>Benign: polyps, inverting papilloma, angiofibroma<br>Malignant: SCC, esthesioneuroblastoma (olfactory neuroblastoma) |
| | Iatrogenic: nasal, sinus, orbit surgery | Inflammation<br>Rhinitis: allergic, non-allergic |
| | Barometric changes | Infections: bacterial, viral, fungal |
| | Nasal dryness: dry air ± septal deformities | Idiopathic |
| | Structural abnormalities:<br>septal deviation, chronic septal perforation | |
| | Chemical: cocaine, nasal sprays, ammonia, etc. | |
| **Systemic** | Coagulopathies<br>Meds: anticoagulants, NSAIDs<br>Hemophilias, von Willebrand disease<br>Hematological malignancies<br>Liver failure, uremia | |
| | Vascular: HTN, atherosclerosis, Osler-Weber-Rendu disease (hereditary hemorrhagic telangectasia) | |
| | Others: GPA, SLE | |



**Special Cases**
- Adolescent male with unilateral recurrent epistaxis: consider juvenile nasopharyngeal angiofibroma (JNA); this is the most common benign tumour of the nasopharynx
- Thrombocytopenic patients: use resorbable packs to avoid risk of re-bleeding caused by pulling out the removable pack

## Investigations
- CBC, PT/PTT (if indicated)
- X-ray, CT as needed

## Treatment
- locate bleeding and achieve hemostasis

## 1. ABCs
- lean patient forward to minimize swallowing blood and avoid airway obstruction
- apply constant firm pressure for 20 min on cartilaginous part of nose (not bony pyramid)
- if significant bleeding, assess vitals for signs of hemorrhagic shock ± IV NS, cross-match blood

## 2. Determine Site of Bleeding
- anterior/posterior hemorrhage defined by location in relationship to bony septum
- visualize nasal cavity with speculum
- use cotton pledget with topical lidocaine ± topical decongestant (i.e. Otrivin®) to help identify area of bleeding (often anterior septum)
- if suspicious of bleeding disorder: coagulation workup (i.e. platelet number and platelet function assay)

## 3. Control the Bleeding
- first-line: topical vasoconstrictors (Otrivin®)
- if first-line fails and bleeding adequately visualized, cauterize with silver nitrate
- **do not cauterize both sides of the septum** at one time due to risk of septal perforation from loss of septal blood supply

**A. Anterior hemorrhage treatment**
- if failure to achieve hemostasis with cauterization
  - place anterior pack* with half inch Vaseline®-soaked ribbon gauze strips layered from nasal floor toward nasal roof and extending to posterior choanae, or lubricated absorbable packing (i.e. Gelfoam wrapped in Surgicel®) for 2-3 d
  - can also attempt packing with Merocel® or nasal tampons of different shapes
  - can also apply Floseal® (hemostatic matrix consisting of topical human thrombin and cross-linked gelatin) if other methods fail

**B. Posterior hemorrhage treatment**
- if unable to visualize bleeding source, then usually posterior source
  - place posterior pack* using a Foley catheter, gauze pack, or Epistat® balloon
  - subsequently, layer anterior packing bilaterally
  - admit to hospital with packs in for 3-5 d
  - watch for complications: hypoxemia (naso-pulmonic reflex), toxic shock syndrome (Rx: remove packs immediately), pharyngeal fibrosis/stenosis, alar/septal necrosis, aspiration

**C. If anterior/posterior packs fail to control epistaxis**
- ligation or embolization of culprit arterial supply by interventional radiology
- ± septoplasty

*antibiotics for any posterior pack or any pack left for >48 h due to risk of toxic shock syndrome

## 4. Prevention
- prevent drying of nasal mucosa with humidifiers, saline spray, or topical ointments
- avoidance of irritants
- medical management of HTN and coagulopathies

# Hoarseness

### Definitions
- hoarseness: change in voice quality, ranging from voice harshness to voice weakness; reflects abnormalities anywhere along the vocal tract from oral cavity to lungs
- dysphonia: a general alteration in voice quality
- aphonia: no sound emanates from vocal folds

If hoarseness present for >2 wk in a smoker, laryngoscopy must be done to rule out malignancy

## Acute Laryngitis

### Definition
- <2 wk inflammatory changes in laryngeal mucosa

### Etiology
- viral: influenza, adenovirus, HSV
- bacterial: Group A *Streptococcus*
- mechanical: acute voice strain → submucosal hemorrhage → vocal cord edema → hoarseness
- environmental: toxic fume inhalation

### Clinical Features
- URTI symptoms, hoarseness, aphonia, cough attacks, ± dyspnea
- true vocal cords erythematous/edematous with vascular injection and normal mobility

### Treatment
- usually self-limited, resolves within ~1 wk
- voice rest
- humidification
- hydration
- avoid irritants (e.g. smoking)
- treat with antibiotics if there is evidence of coexistent bacterial pharyngitis

**Vocal Cord Paralysis**
**Unilateral**: Affected cord lies in the paramedian position, inadequate glottic closure during phonation → weak, breathy voice. Usually medializes with time, whereby phonation and aspiration improve. Treatment options include voice therapy, injection laryngoplasty (Radiesse), medialization using silastic block

**Bilateral**: Cords rest in midline, therefore voice remains good but respiratory function is compromised and may present as stridor. If no respiratory issues, may monitor closely and wait for improvement. If respiratory issues, intubate and will likely require vocal cord lateralization, arytenoidectomy, posterior costal cartilage graft, or tracheotomy

## Chronic Laryngitis

### Definition
- >2 wk inflammatory changes in laryngeal mucosa

### Etiology
- repeated attacks of acute laryngitis
- chronic irritants (dust, smoke, chemical fumes)
- chronic voice strain
- chronic rhinosinusitis with postnasal drip
- chronic EtOH use
- esophageal disorders: GERD, Zenker's diverticulum, hiatus hernia
- systemic: allergy, hypothyroidism, Addison's disease

### Clinical Features
- chronic dysphonia: rule out malignancy
- cough, globus sensation, frequent throat clearing 2° to GERD
- laryngoscopy: erythematous and thickened cords with ulceration/granuloma formation and normal mobility

### Treatment
- remove offending irritants
- treat related disorders (e.g. antisecretory therapy for GERD)
- speech therapy with voice rest
- ± antibiotics ± steroids to decrease inflammation
- laryngoscopy to rule out malignancy

## Vocal Cord Polyps

### Definition
- structural manifestation of vocal cord irritation
- acutely, polyp forms 2° to capillary damage in the subepithelial space during extreme voice exertion

### Etiology
- most common benign tumour of vocal cords
- voice strain (i.e. muscle tension dysphonia)
- laryngeal irritants (i.e. GERD, allergies, tobacco)

### Epidemiology
- 30-50 yr of age
- M>F

### Clinical Features
- hoarseness, aphonia, cough attacks ± dyspnea
- pedicled or sessile polyp on free edge of vocal cord
- typically, polyp is asymmetrical, soft, and smooth
- more common on the anterior 1/3 of the vocal cord
- intermittent respiratory distress with large polyps

### Treatment
- avoid irritants
- endoscopic laryngeal microsurgical removal if persistent or if high risk of malignancy

## Vocal Cord Nodules

### Definition
- vocal cord callus
- i.e. "screamer's" or "singer's" nodules

### Etiology
- early nodules occur 2° to submucosal hemorrhage
- mature nodules result from hyalinization, which occurs with long-term voice abuse
- chronic voice strain
- frequent URTI, smoking, EtOH consumption

### Epidemiology
- frequently in singers, children, bartenders, and school teachers
- F>M

### Clinical Features
- hoarseness worst at end of day
- on laryngoscopy
  - often bilateral
  - at the junction of the anterior 1/3 and posterior 2/3 of the vocal cords – point of maximal cord vibration
- chronic nodules may become fibrotic, hard, and white

### Treatment
- voice rest
- hydration
- speech therapy
- avoid irritants
- surgery rarely indicated for refractory nodules

**Vocal Cords: Polyps vs. Nodules**

| Polyps | Nodule |
|---|---|
| Unilateral, asymmetric | Bilateral |
| Acute onset | Gradual onset |
| May resolve spontaneously | Often follow a chronic course |
| Subepithelial capillary breakage | Acute: submucosal hemorrhage or edema<br>Chronic: hyalinization within submucosal lesion |
| Soft, smooth, fusiform, pedunculated mass | Acute: small, discrete nodules<br>Chronic: hard, white, thickened fibrosed nodules |
| Proton pump inhibitor | Voice rest but no whispering, hydration, speech therapy if refractory to therapy |
| Surgical excision if persistent or in the presence of risk factors for laryngeal cancer | Surgical excision as last resort |

## Benign Laryngeal Papillomas

### Etiology
- HPV types 6, 11
- possible hormonal influence, possibly acquired during delivery

### Epidemiology
- biphasic distribution: 1) birth to puberty (most common laryngeal tumour) and 2) adulthood

### Clinical Features
- hoarseness and airway obstruction
- can seed into tracheobronchial tree
- highly resistant to complete removal
- some juvenile papillomas resolve spontaneously at puberty
- may undergo malignant transformation
- laryngoscopy shows wart-like lesions in supraglottic larynx and trachea

### Treatment
- microdebridement or $CO_2$ laser
- adjuvants under investigation: interferon, cidofovir, acyclovir
- HPV vaccine may prevent/decrease the incidence, but more research is needed

## Laryngeal Carcinoma

- see *Neoplasms of the Head and Neck*, OT34

# Salivary Glands

## Sialadenitis

### Definition
- inflammation of salivary glands

### Etiology
- viral most common (mumps)
- bacterial causes: *S. aureus, S. pneumoniae, H. influenzae*
- obstructive vs. non-obstructive
  - obstructive infection involves salivary stasis and bacterial retrograde flow

### Predisposing Factors
- HIV
- anorexia/bulimia
- Sjögren's syndrome
- Cushing's syndrome, hypothyroidism, DM
- hepatic/renal failure
- meds that increase stasis: diuretics, tricyclic antidepressants, β-blockers, anticholinergics, antibiotics
- sialolithiasis (can cause chronic sialadenitis)

Bilateral enlargement of the parotid glands may be a manifestation of a systemic disease, such as mumps, HIV, Sjögren's, or an eating disorder (i.e. anorexia, bulimia)

### Clinical Features
- acute onset of pain and edema of parotid or submandibular gland that may lead to marked swelling
- ± fever
- ± leukocytosis
- ± suppurative drainage from punctum of the gland

Mumps usually presents with bilateral parotid enlargement ± SNHL ± orchitis

### Investigations
- U/S imaging to differentiate obstructive vs. non-obstructive sialadenitis

### Treatment
- bacterial: treat with cloxacillin ± abscess drainage, sialogogues
- viral: no treatment

## Sialolithiasis

### Definition
- ductal stone (mainly hydroxyapatite in adults, sand/sludge in children), leading to chronic sialadenitis
- 80% in submandibular gland, <20% in parotid gland, ~1% in sublingual gland

### Risk Factors
- any condition causing duct stenosis or a change in salivary secretions (e.g. dehydration, diabetes, EtOH, hypercalcemia, psychiatric medications)

### Clinical Features
- pain and tenderness over involved gland
- intermittent swelling related to meals
- digital palpation reveals presence of calculus

### Investigations
- U/S ± sialogram

### Treatment
- may resolve spontaneously
- encourage salivation to clear calculus
- massage, analgesia, antibiotics, sialogogues (e.g. lemon wedges, sour lemon candies), warm compresses
- remove calculi endoscopically, by dilating duct or orifice, or by excision through floor of the mouth
- gland-preserving surgery has long-term symptom improvement and favourable gland retention rates

## Salivary Gland Neoplasms

### Etiology
- anatomic distribution
  - parotid gland: 70-85%
  - submandibular gland: 8-15%
  - sublingual gland: 1%
  - minor salivary glands, most concentrated in hard palate: 5-8%

- malignant (see Table 15 and Table 16, OT35)
- benign
  - benign mixed (pleomorphic adenoma): 80%
  - Warthin's tumour (5-10% bilateral, M>F): 10%
  - cysts, lymph nodes, and adenomas: 10%
  - oncocytoma: <1%

### Epidemiology
- 3-6% of all head and neck neoplasms in adults
- mean age at presentation: 55-65
- M=F

A mass sitting above an imaginary line drawn between the mastoid process and angle of the mandible is a parotid neoplasm until proven otherwise

## Parotid Gland Neoplasms

### Clinical Features
- 80% benign (most common: pleomorphic adenoma), 20% malignant (most common: mucoepidermoid)
- if bilateral, suggests benign process (e.g. Warthin's tumour, Sjögren's, bulimia, mumps) or possible lymphoma
- facial nerve involvement (e.g. facial paralysis) increases risk of malignancy

**DDx Parotid Tumour**

**Benign**
- Pleomorphic adenoma
- Warthin's tumour (more common in men)
- Benign lymphoepithelial cysts (viral eitiology e.g. HIV)
- Oncocytoma

**Malignant**
- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Acinic cell carcinoma

### Investigations
- FNA biopsy
- CT, U/S, or MRI to determine extent of tumour

### Treatment
- treatment of choice is surgery for all salivary gland neoplasms – benign and malignant
- pleomorphic adenomas are excised due to risk of malignant transformation (5% risk over prolonged period of time)
- superficial tumour
  - superficial parotidectomy above plane of CN VII ± radiation
  - incisional biopsy contraindicated
- deep lesion
  - near-total parotidectomy sparing as much of CN VII as possible
  - if CN VII involved, then it is removed and cable grafted
- complications of parotid surgery
  - hematoma, infection, salivary fistula, temporary facial paresis, Frey's syndrome (gustatory sweating)

Frey's syndrome is a post-operative complication characterized by gustatory sweating. It is due to aberrant innervation of cutaneous sweat glands by parasympathetic nerve fibres that are divided during surgery

### Prognosis
- benign: excellent, <5% of pleomorphic adenomas recur
- malignant: dependent on stage and type of malignancy (see Table 16, OT35)

# Neck Masses

## Approach to a Neck Mass

- ensure that the neck mass is not a normal neck structure (e.g. hyoid, transverse process of C1 vertebra, prominent carotid bulb)
- any neck mass persisting for >2 wk should be investigated for possible neoplastic causes

**Table 15. Prevalence of Acquired Causes of Neck Lumps According to Age**

| Age (yr) | Possible Causes of Neck Lump | | |
|---|---|---|---|
| <40 | 1. Inflammatory | 2. Congenital/Developmental | 3. Neoplastic |
| >40 | 1. Neoplastic | 2. Inflammatory | 3. Congenital |

### Differential Diagnosis
- congenital
  - lateral (branchial cleft cyst, laryngocele, plunging ranula, lymphatic/venous/venolymphatic malformation)
  - midline (thyroglossal duct cyst, dermoid cyst, teratoma, thyroid/thymus anomaly, vascular malformation)
- infectious/inflammatory
  - reactive lymphadenopathy (2° to tonsillitis, pharyngitis)
  - infectious mononucleosis
  - Kawasaki, Kikuchi-Fujimoto, Kimura, Cat-scratch, Castleman, Rosai-Dorfman disease
  - HIV
  - sialolithiasis, sialadenitis
  - thyroiditis

- granulomatous disease
  - mycobacterial infections
  - sarcoidosis
- neoplastic
  - lymphoma
  - salivary gland tumours
  - thyroid tumours
  - metastatic malignancy ("unknown primary")
  - lipoma, fibroma, hemangioma, nerve or nerve sheath tumour

## Evaluation

### Investigations

- history and physical (including nasopharynx and larynx)
- all other investigations and imaging are dependent upon clinical suspicion following history and physical
- laboratory investigations
  - WBC: infection vs. lymphoma
  - Mantoux TB test
  - thyroid function tests and scan
- imaging
  - neck U/S
  - CT scan
  - angiography: vascularity and blood supply to mass
- biopsy for histologic examination
  - FNA: least invasive
  - needle biopsy
  - open biopsy for lymphoma
- identification of possible primary tumour (rule out a metastatic lymph node from an unknown primary)
  - panendoscopy: nasopharyngoscopy, laryngoscopy, esophagoscopy, bronchoscopy with washings, and biopsy of suspicious lesions
  - biopsy of normal tissue of nasopharynx, tonsils, base of tongue, and hypopharynx
  - primary identified 95% of time → stage and treat
  - primary occult identified 5% of time: excisional biopsy of node for histologic diagnosis → manage with radiotherapy and/or neck dissection (squamous cell carcinoma)

**Inflammatory vs. Malignant Neck Masses**

| | Inflammatory | Neoplastic |
|---|---|---|
| **History** | | |
| Painful | Y | N |
| H&N infection | Y | N |
| Fever | Y | N |
| Weight loss | N | Y |
| CA risk factors | N | Y |
| Age | Younger | Older |
| **Physical** | | |
| Tender | Y | N |
| Rubbery | Y | Occipital |
| Rock hard | N | Y |
| Mobile | Y | ± fixed |

# Congenital Neck Masses

## Brachial Cleft Cysts/Sinuses/Fistulae

### Embryology

- at the 6th wk of development, the 2nd branchial arch grows over the 3rd and 4th arches and fuses with the neighbouring caudal pre-cardial swelling, forming the cervical sinus
- 3 types of malformations
  1. branchial fistula: persistent communication between skin and GI tract
  2. branchial sinus: blind-ended tract opening to skin
  3. branchial cyst: persistent cervical sinus with no external opening

### Clinical Features

- 2nd branchial cleft malformations most common
  - sinuses and fistulae present in infancy as a small opening anterior to the sternocleidomastoid muscle
  - cysts present as a smooth, painless, slowly enlarging lateral neck mass, often following a URTI
- 1st branchial cleft malformations present as sinus/fistula or cyst in preauricular area or on face over angle of mandible
- 3rd branchial cleft malformations present as recurrent thyroiditis or thyroid abscess and have a tract which usually leads to the left pyriform sinus. Air on CT scan in or near the thyroid gland is pathognomonic for this anomaly
- there is controversy whether 4th branchial cleft anomalies exist, as they may be remnants of the thyrothymic axis

### Treatment

- surgical removal of cyst or fistula tract
- if infected: allow infection to settle before removal (antibiotics may be required)

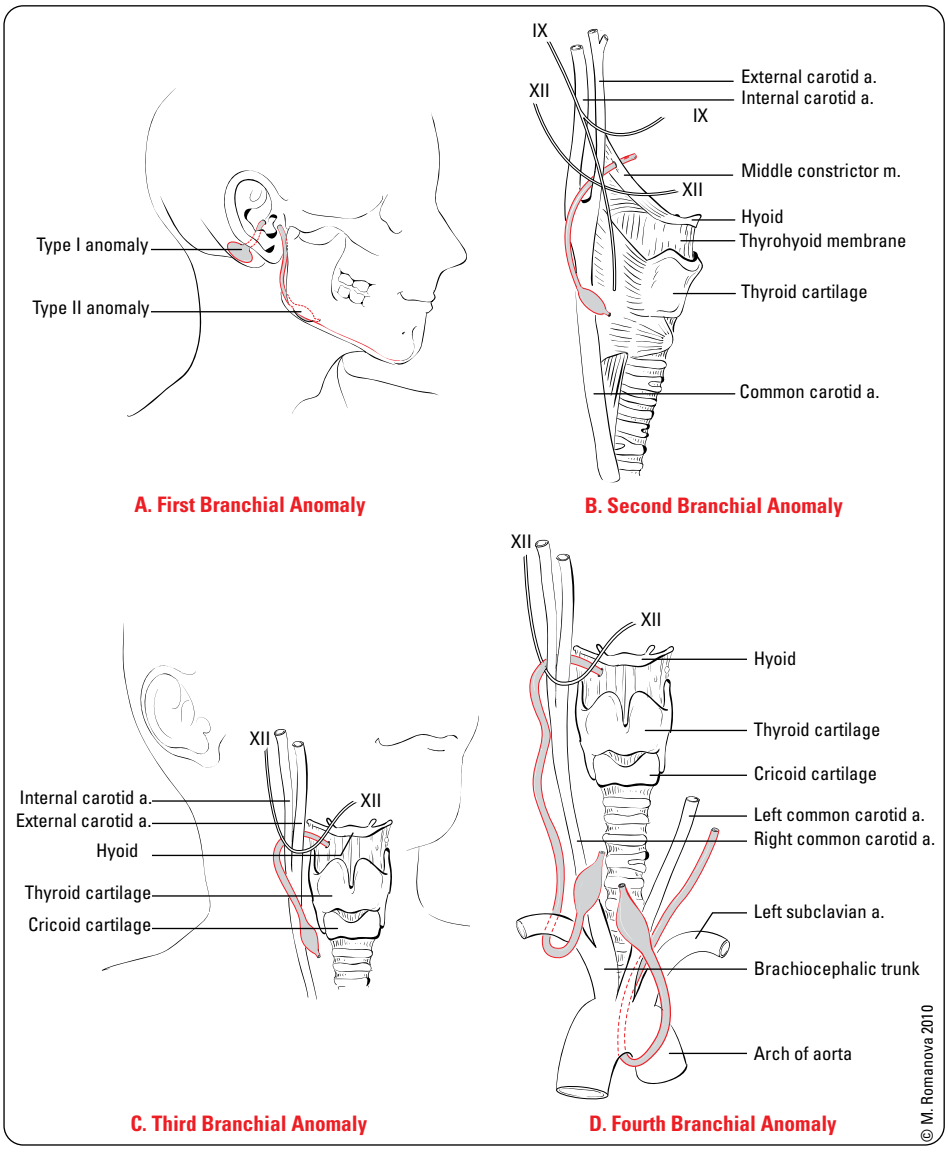



**Figure 19. Branchial cleft anomalies**

# Thyroglossal Duct Cysts

## Embryology

- thyroid originates as ventral midline diverticulum at base of tongue, caudal to junction of 3rd and 4th branchial arches (foramen cecum), and migrates down to inferior aspect of neck
- thyroglossal duct cysts are vestigial remnants of this tract

## Clinical Features

- usually presents in childhood or during 20-40 s as a midline cyst that enlarges with URTI and elevates with swallowing and tongue protrusion

## Treatment

- pre-operative antibiotics to reduce inflammation (infection before surgery is a well-described cause of recurrence)
- small potential for neoplastic transformation, so complete excision of cyst and tissue around tract up to foramen cecum at base of tongue, with removal of central portion of hyoid bone (Sistrunk procedure) recommended

# Lymphatic, Venous, or Mixed Venolymphatic Malformations

### Definition
- lymphatic malformation arising from vestigial lymph channels of neck

### Clinical Features
- commonly identified in many fetuses, but regress before birth and never cause a clinical problem
- usually present by age 2
- can be macrocystic (composed of large, thin-walled cysts, usually below level of mylohyoid muscle) or microcystic (composed of minute cysts, usually above level of mylohyoid muscle)
- usually painless, soft, compressible
- infection or trauma causes a sudden increase in size

### Treatment
- can regress spontaneously after bacterial infection, therefore do not plan surgical intervention until several months after infection
- macrocystic lesions can be treated by sclerotherapy or surgical excision
- microcystic lesions are difficult to treat, but can be debulked if it will not cause loss of function of normal structures, or injected with sclerotherapy in surrounding tissues

# Neoplasms of the Head and Neck

### Pre-Malignant Disease
- leukoplakia
  - hyperkeratosis of oral mucosa
  - risk of malignant transformation 5-20%
- erythroplakia
  - red superficial patches adjacent to normal mucosa
  - commonly associated with epithelial dysplasia
  - associated with carcinoma *in situ* or invasive tumour in 40% of cases
- dysplasia
  - histopathologic presence of mitoses and prominent nucleoli
  - involvement of entire mucosal thickness = carcinoma *in situ*
  - associated progression to invasive cancer in 15-30% of cases

### Investigations
- initial metastatic screen includes CXR
- scans of liver, brain, and bone only if clinically indicated
- CT scan is superior to MRI for the detection of pathologic nodal disease and bone cortex invasion
- MRI is superior to discriminate tumour from mucus and to detect bone marrow invasion
- ± PET scans
- endoscopy with biopsy

### Treatment
- treatment depends on:
  - histologic grade of tumour
  - stage
  - physical and psychological health of patient
  - facilities available
  - expertise and experience of the medical and surgical oncology team
- in general:
  - 1° surgery for malignant oral cavity tumours with radiotherapy reserved for salvage or poor prognostic indicators
  - 1° radiotherapy for nasopharynx, oropharynx, hypopharynx, and larynx malignancies with surgery reserved for salvage, although laser endoscopic surgery for early stage larynx cancer is an option and 1° surgery for advanced (T4) pharyngeal and laryngeal cancer is the standard of care
  - there is an emerging role for primary surgery (transoral robotic surgery [TORS]) for oropharyngeal cancer
  - palliative chemotherapy for metastatic or incurable disease
  - concomitant chemotherapy increases survival in advanced disease
  - chemotherapy has a role as induction therapy prior to surgery and radiation
  - panendoscopy to detect primary disease when lymph node metastasis is identified
  - anti-epidermal growth factor receptor treatment (cetuximab, panitumumab) has a role as concurrent therapy with radiation for SCC of the head and neck (for advanced local and regional disease)

### Prognosis
- synchronous tumours occur in 9-15% of patients
- late development of 2nd primary is most common cause of post-treatment failure after 36 mo



All patients presenting with a head and neck mass should be asked if they are experiencing the following obstructive, referred, or local symptoms
- Oropharyngeal: Odynophagia, dysphagia, non-healing oral ulcers
- Otologic: Otalgia, hearing loss
- Laryngeal: Dyspnea or stridor (position vs. non-positional), hoarseness, dysphonia → positional vs. non-positional
- Nasopharyngeal: Recurrent epistaxis, unilateral nasal obstruction, persistent rhinorrhea or sinusitis
- Hemoptysis, hematemesis



Detection of cervical lymph nodes on physical exam
- False negative rate: 15-30%
- False positive rate: 30-40%



Pathological lymphadenopathy defined radiographically as
- A jugulodigastric node >1.5 cm in diameter, or a retropharyngeal node >1 cm in diameter
- A node of any size which contains central necrosis



Common sites of distant metastases for head and neck neoplasms
lungs > liver > bones



**Risk Factors for Head and Neck Cancer**
- Smoking
- EtOH (synergistic with smoking)
- Radiation
- Occupational/environmental exposures
- Oral HPV infection (independent of smoking and EtOH exposure)
- Family history of cancer
- Previous cancer



The smaller the salivary gland, the greater the likelihood that a mass in the gland is malignant

**Table 16. Quick Look-Up Summary of Head and Neck Malignancies – Etiology and Epidemiology**

| Etiology | Epidemiology | Risk Factors |
|---|---|---|
| **Oral Cavity** | | |
| 95% SCC<br>Others: sarcoma, melanoma, minor salivary gland tumour | Mean age: 50-60 yr<br>M>F<br>Most common site of H&N cancers<br>50% on anterior 2/3 of tongue | Smoking/EtOH<br>Poor oral hygiene<br>Leukoplakia, erythroplakia<br>Lichen planus, chronic inflammation<br>Sun exposure – lip<br>HPV infection<br>Plummer-Vinson syndrome |
| **Nose and Paranasal Sinus** | | |
| 75-80% SCC<br>Adenocarcinoma (2nd most common) and mucoepidermoid<br>99% in maxillary/ethmoid sinus<br>10% of nose and paranasal sinus tumours arise from minor salivary glands | Mean age: 50-70 yr<br>Rare tumours<br>↓ incidence in last 5-10 yr | Wood/shoe/textile industry<br>Hardwood dust (nasal/ethmoid sinus)<br>Nickel, chromium (maxillary sinus)<br>Air pollution<br>Chronic rhinosinusitis |
| **Carcinoma of the Pharynx – Subtypes (Nasopharynx, Oropharynx, Hypopharynx, and Larynx)** | | |
| **Nasopharynx** | | |
| 90% SCC<br>~10% lymphoma | Mean age: 50-59 yr<br>M:F= 2.4:1<br>Incidence 0.8 per 100,000<br>100x increased incidence in Southern Chinese | Epstein-Barr virus (EBV)<br>Salted fish<br>Nickel exposure<br>Poor oral hygiene<br>Genetic – Southern Chinese |
| **Oropharynx** | | |
| 95% SCC – poorly differentiated<br>Up to 70% of oropharnyngeal cancer (OPC) attributable to HPV | Mean age: 50-70 yr<br>Patients with HPV+ OPC are approximately 10 yr younger<br>Prevalence of HPV+ OPC has increased by 225% from 1988 to 2004<br>M:F = 4:1 | Smoking/EtOH<br>HPV 16 infection: increased sexual encounters, specifically oral sex |
| **Hypopharynx** | | |
| 95% SCC<br>3 sites<br>1. pyriform sinus (60%)<br>2. postcricoid (30%)<br>3. posterior pharyngeal wall (10%) | Mean age: 50-70 yr<br>M>F<br>8-10% of all H&N cancer | Smoking/EtOH |
| **Larynx** | | |
| SCC most common<br>3 sites<br>1. supraglottic (30-35%)<br>2. glottic (60-65%)<br>3. subglottic (1%) | Mean age: 45-75 yr<br>M:F = 10:1<br>45% of all H&N cancer | Smoking/EtOH<br>HPV 16 infection strongly associated with the risk of laryngeal squamous cell cancers |
| **Salivary Gland** | | |
| 40% mucoepidermoid<br>30% adenoid cystic<br>5% acinic cell<br>5% malignant mixed<br>5% lymphoma | Mean age: 55-65 yr<br>M=F<br>3-6% of all H&N cancer<br>Percentage of malignant tumours in each gland:<br>Parotid 15-25%<br>Submandibular 37-43%<br>Minor salivary >80% | |
| **Thyroid (90% benign – 10% malignant)** | | |
| >80% papillary<br>5-15% follicular<br>5% medullary<br><5% anaplastic<br>1-5% Hürthle cell<br>1-2% metastatic | Children<br>Adults <30 or >60 yr<br>Nodules more common in females<br>Malignancy more common in males | Radiation exposure<br>Family history – papillary CA or multiple endocrine neoplasia (MEN II)<br>Older age<br>Male<br>Papillary – Gardner's syndrome, Cowden syndrome, familial adenomatous polyposis (FAP) |
| **Parathyroid** | Mean age: 44-55 yr<br>Rare tumour | |

**Survival Comparison between HPV Positive and HPV Negative Head and Neck Squamous Cell Carcinoma**
Int J Cancer 2007;121(8):1813-20
**Summary**: HPV positive oropharyngeal cancer has better prognosis vs. HPV negative oropharyngeal cancer. It may be a good idea to routinely test for HPV status for all adult patients presenting with oropharyngeal squamous cell carcinoma.
**Results**: Meta-analysis on relationship between HPV infection and overall survival and disease-free survival in head and neck squamous cell carcinoma. Site-specific analysis for oropharyngeal tumours show that HPV positive group has 28% reduced risk of death (HR 0.72, 95% CI: 0.5-1.0). Similar observations were made for disease-free status (HR: 0.51, 95% CI 0.4-0.7).

**Chemoradiotherapy for Advanced Head and Neck Squamous Cell Carcinoma (HNSCC)**
Radiother Oncol 2009;92(1):4-14
**Summary**: Cisplatin monochemotherapy or 5-fluorouracil (5-FU) plus cisplatin polychemotherapy should be used in treatment of HNSCC. Concomitant chemotherapy has higher benefit than neo-adjuvant chemotherapy.
**Results**: Meta-analysis including 87 trials (16,485 patients) comparing regional treatment vs. regional treatment plus chemotherapy in HNSCC patients. Cisplatin monochemotherapy or 5-FU plus cisplatin polychemotherapy had the highest effect of chemotherapy. Both direct and indirect comparisons showed a more pronounced benefit of concomitant chemotherapy (HR 0.81, absolute benefit 6.5% at 5 years) vs. neo-adjuvant chemotherapy (HR 0.88, absolute benefit 4.5% at 5 years). There is no good evidence for adjuvant chemotherapy (HR 1.06, p=0.32).

**Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study**
Lancet 2019. 393(10167): 156-167
**Objective**: Compare the efficacy and safety of pembrolizumab versus standard-of-care therapy for the treatment of head-and-neck squamous cell carcinoma.
**Study**: Randomised, open-label, phase 3 clinical trial.
**Patients**: 495 patients randomized to either pembrolizumab or standard-of-care treatment groups.
**Results**: Median overall survival was 8.4 mo (95% CI 6.4–9.4) with pembrolizumab and 6.9 mo (5.9–8.0) with standard of care (HR 0.80, 0.65–0.98; p=0.0161). Fewer patients treated with pembrolizumab than with standard-of-care had grade 3 or worse treatment-related adverse events (33 [13%] of 246 vs. 85 [36%] of 234). Four treatment-related deaths with pembrolizumab vs. two for standard-of-care.
**Conclusion**: Pembrolizumab treatment prolongs overall survival and has a more favourable safety profile when compared to standard treatment for recurrent or metastatic head and neck squamous cell carcinoma.

**Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck**
NEJM 2016;375:1856-1867
**Objective**: To assess whether overall survival would be longer with nivolumab therapy than with standard therapy in patients with platinum-refractory head and neck squamous-cell carcinoma.
**Study**: Randomized, open-label, phase 3 clinical trial.
**Patients**: 361 patients with recurrent head and neck squamous-cell carcinoma whose disease had progressed within 6 mo after platinum-based chemotherapy.
**Results**: The median overall survival was 7.5 mo in the nivolumab group vs. 5.1 mo in the standard therapy group. Overall survival was significantly longer with nivolumab. No difference in median progression-free survival, but the rate of progression-free survival at 6 mo was 19.7% with nivolumab vs. 9.9% with standard therapy. Treatment-related adverse events of grade 3 or 4 occurred in 13.1% of the patients in the nivolumab group vs. 35.1% of those in the standard-therapy group.
Conclusion: Treatment with nivolumab resulted in longer overall survival, overall progression-free survival, and fewer adverse events than treatment with standard therapy.

**Table 17. Quick Look-Up Summary of Head and Neck Malignancies – Diagnosis and Treatment**

| Clinical Features | Investigations | Treatment | Prognosis |
|---|---|---|---|
| **Oral Cavity** | | | |
| Asymptomatic neck mass (30%)<br>Non-healing ulcer ± bleeding<br>Dysphagia, sialorrhea, dysphonia<br>Oral fetor, otalgia, leukoplakia, or erythroplakia (pre-malignant changes or clinically isolated syndrome) | Biopsy<br>CT | 1° surgery<br>local resection<br>± neck dissection<br>± reconstruction<br>2° radiation | 5 yr overall survival<br>T1/T2: 75%<br>T3/T4: 30-35%<br>Poor prognostic indicators<br>Depth of invasion, close surgical margins location (tongue worse than floor of mouth)<br>Cervical nodes, extra-capsular spread |
| **Nose and Paranasal Sinus** | | | |
| **Early Symptoms**<br>Unilateral nasal obstruction<br>Epistaxis, rhinorrhea<br>**Late Symptoms**<br>2° to invasion of nose, orbit, nerves, oral cavity, skin, skull base, cribriform plate | CT/MRI<br>Biopsy | Surgery and radiation<br>Chemoradiotherapy | 5 yr survival: 30-60%<br>Poor prognosis 2° to late presentation |
| **Nasopharynx** | | | |
| Cervical nodes (60-90%)<br>Nasal obstruction, epistaxis<br>Unilateral otitis media ± hearing loss<br>CN III to VI, IX to XII (25%)<br>Proptosis, voice change, dysphagia | Nasopharyngoscopy<br>Biopsy<br>CT/MRI | 1° radiation ± chemoradiation<br>Surgery for limited or recurrent disease | 5 yr survival<br>T1: 79%<br>T2: 72%<br>T3: 50-60%<br>T4: 36-42% |
| **Oropharynx** | | | |
| Odynophagia, otalgia<br>Ulcerated/enlarged tonsil<br>Fixed tongue/trismus/dysarthria<br>Oral fetor, bloody sputum<br>HPV+ OPC predominantly arises at base of tongue or tonsillar region<br>Cervical lymphadenopathy (60%)<br>Distant mets: lung/bone/liver (7%) | Biopsy<br>Determine HPV status via RT=PCR: positive if presence of HPV DNA and p16 overexpression<br>CT | 1° radiation<br>2° surgery<br>local resection<br>±neck dissection<br>±reconstruction | 5 yr overall survival<br>Stratified by TMN stage (I, II, III, IV)<br>HPV negative OPC (70%, 58%, 50%, 30%)<br>HPV positive OPC (88%, 78%, 71%, 74%)<br>HPV positive OPC further stratified by stage, age, and smoking pack years (PY)<br>group I (T1-3N0-N2c, ≤20 PY): 89%<br>group II (T1-3N0-N2c, >20 PY): 64%<br>group III (T4 or N3, age ≤70): 57%<br>group IVA (T4 or N3, age >70): 40% |
| **Hypopharynx** | | | |
| Dysphagia, odynophagia<br>Otalgia, hoarseness<br>Cervical lymphadenopathy | Pharyngoscopy<br>Biopsy<br>CT | 1° radiation<br>2° surgery | 5 yr survival<br>T1: 53%<br>T2/T3: 36-39%<br>T4: 24% |
| **Larynx** | | | |
| Dysphagia, odynophagia, globus<br>Otalgia, hoarseness<br>Dyspnea/stridor<br>Cough/hemoptysis<br>Cervical nodes (rare with glottic CA) | Laryngoscopy<br>CT/MRI | 1° radiation<br>2° surgery<br>1° surgery for bulky T4 disease | 5 yr survival<br>T4: >40% (surgery with radiation)<br>Control rate early lesions: >90% (radiation)<br>10 to 12% of small lesions fail radiotherapy |
| **Salivary Gland** | | | |
| Painless mass (occ. pain is possible)<br>CN VII palsy<br>Cervical lymphadenopathy<br>Rapid growth<br>Invasion of skin<br>Constitutional signs/symptoms | FNA<br>MRI/CT/U/S | 1° surgery ± neck dissection<br>Post-operative radiotherapy<br>Chemotherapy if unresectable | Parotid<br>10 yr survival: 85, 69, 43, and 14% for stages T1 to T4<br>Submandibular<br>2 yr survival: 82%, 5 yr: 69%<br>Minor salivary gland<br>10 yr survival: 83, 52, 25, 23% for stages T1 to T4 |
| **Thyroid** | | | |
| Thyroid mass, cervical nodes<br>Vocal cord paralysis<br>Hyper/hypothyroidism<br>Dysphagia | FNA<br>U/S | 1° surgery<br>$I^{131}$ for intermediate and high-risk well-differentiated thyroid cancer | Recurrences occur within 5 yr<br>Need long-term follow-up: clinical exam, thyroglobulin |
| **Parathyroid** | | | |
| Increased serum $Ca^{2+}$<br>Neck mass<br>Bone disease, renal disease<br>Pancreatitis | Sestamibi | Wide surgical excision<br>Post-operative monitoring of serum $Ca^{2+}$ | Recurrence rates<br>1 yr: 27%<br>5 yr: 82%<br>10 yr: 91%<br>Mean survival: 6-7 yr |

# Thyroid Carcinoma

### Table 18. Bethesda Classification of Thyroid Cytology

| Diagnostic Category | Risk of Malignancy if NIFTP is not considered Cancer | Risk of Malignancy if NIFTP is considered Cancer |
|---|---|---|
| Non-diagnostic or unsatisfactory | 5-10% | 5-10% |
| Benign | 0-3% | 0-3% |
| Follicular lesion of undetermined significance/Atypia of undetermined significance | 6-18% | 10-30% |
| Follicular neoplasm or suspicious for a follicular neoplasm | 10-40% | 25-40% |
| Suspicious for malignancy | 45-60% | 50-75% |
| Malignant | 94-96% | 97-99% |

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) is a reporting system for thyroid FNA. The 2017 revision introduces the reclassification of noninvasive follicular variant of papillary thyroid carcinoma as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).

### Table 19. Thyroid Carcinoma

| | Papillary | Follicular | Medullary | Anaplastic | Lymphoma |
|---|---|---|---|---|---|
| **Incidence (% of all thyroid cancers)** | 70-80% | 10-15% | 1 to 2%<br>(90% sporadic, 10% familial – test for RET germline mutation) | <2% | <1% |
| **Route of Spread** | Lymphatic | Hematogenous | Lymphatic and hematogenous | N/A | |
| **Histology** | Orphan Annie nuclei<br>Psammoma bodies<br>Papillary architecture | Capsular/vascular invasion<br>Invasion influences prognosis | Amyloid<br>May secrete calcitonin, prostaglandins, ACTH, serotonin, kallikrein, or bradykinin | Giant cells<br>Spindle cells | |
| **Other** | **P**s – **P**apillary cancer<br>**P**opular (most common)<br>**P**alpable lymph nodes<br>**P**ositive $I^{131}$ uptake<br>**P**ositive prognosis<br>**P**ost-operative $I^{131}$ scan to guide treatments | **F**s – **F**ollicular cancer<br>**F**ar away mets<br>**F**emale (3:1)<br>NOT FNA (cannot be diagnosed by **F**NA)<br>**F**avourable prognosis | **M**s – **M**edullary cancer<br>**M**ultiple endocrine neoplasia (**M**EN IIa or IIb)<br>a**M**yloid<br>**M**edian node dissection | More common in elderly<br>70% in women<br>20-30% have Hx of differentiated thyroid CA (mostly papillary) or nodular goitre mass<br>Rapidly enlarging neck<br>Rule out lymphoma | Usually non-Hodgkin's lymphoma<br>Rapidly enlarging thyroid mass<br>Hx of Hashimoto's thyroiditis increases risk 60x<br>4:1 female predominance<br>dysphagia, dyspnea, stridor, hoarseness, neck pain, facial edema, accompanied by "B" symptoms* |
| **Prognosis** | 98% at 10 yr | 92% at 10 yr | 50% at 10 yr<br>20% at 10 yr if detected when clinically palpable | 20-35% at 1 yr<br>13% at 10 yr | 5 yr survival<br>Stage IE: 55%-80%<br>Stage IIE: 20%-50%<br>Stage IIE/IV: 15%-35% |
| **Treatment** | Small tumours: Near total thyroidectomy or lobectomy<br>Diffuse/bilateral: Total thyroidectomy<br>± neck dissection ± post-operative $I^{131}$ treatment | Small tumours: Near total thyroidectomy/lobectomy/isthmectomy<br>Large/diffuse tumours: Total thyroidectomy | Total thyroidectomy<br>Median and/or lateral compartment node neck dissection (based on serum calcitonin)<br>Modified neck dissection<br>Post-operative thyroxine, radiotherapy<br>Tracheostomy<br>Screen relatives | Subtotal thryoidectomy, radiation, chemotherapy, palliative care<br>Small tumours:<br>Total thyroidectomy<br>± external beam | Non-surgical<br>Combined radiation<br>Chemotherapy (CHOP**) |

*B symptoms = fever, night sweats, chills, weight loss >10% in 6 mo ** CHOP = cyclophosphamide, adriamycin, vincristine, prednisone

## Approach to Thyroid Nodule

- all patients with thyroid nodules require evaluation of serum TSH and ultrasound
- intermediate-high suspicion nodule >1 cm and low suspicion nodule >1.5 cm should undergo FNA
- nodules <1 cm with clinical symptoms or lymphadenopathy may require further evaluation
- when performing repeat FNA on initially non-diagnostic nodules, U/S-guided FNA should be employed
- nuclear scanning has minimal value in the investigation of the thyroid nodule
- molecular testing is increasingly used to identify gene mutations associated with thyroid cancers to determine "high risk" from "low risk" thyroid nodules

### Table 20. Management of the Thyroid Nodule

| Treatment | Indications |
|---|---|
| Radioiodine therapy | Treatment of hyperthyroidism<br>After surgery as adjuvant treatment of intermediate-high risk papillary or follicular carcinoma |
| Chemotherapy and/or radiotherapy | Recurrent/residual medullary CA, anaplastic CA or thyroid lymphoma |
| Surgical excision | Nodule that is suspicious on FNA cytology<br>Malignancy other than anaplastic CA or thyroid lymphoma<br>Mass that is benign on FNA but increasing in size on serial imaging and/or >3-4 cm in size<br>Hyperthyroidism not amenable to medical therapy |

***U/S findings:** cystic: risk of malignancy <1%; solid: risk of malignancy ~10%; solid with cystic components: risk of malignancy same as if solid

**Indications for Post-Operative Radioactive Iodine Ablation – $I^{131}$**
Adjuvant therapy: decrease recurrent disease
Radioactive Iodine (RAI) therapy: treat persistent cancer

# Pediatric Otolaryngology

## Acute Otitis Media

### Definition
- all of: presence of middle ear effusion (MEE); presence of middle ear inflammation (MEI); acute onset of symptoms of MEE and MEI

### Epidemiology
- most frequent diagnosis in sick children visiting clinicians' offices and most common reason for antibiotic administration
- peak incidence between 6-15 mo: ~85% of children have >1 episode by 3 yr old
- seasonal variability: peaks in winter

### Etiology
- primary defect causing AOM: Eustachian tube dysfunction/obstruction → stasis/colonization by pathogens
- bacterial: *S. pneumoniae*, non-typable *H. influenzae, M. catarrhalis*, group A *Streptococcus*, *S. aureus*
- viral: RSV, influenza, parainfluenza, adenovirus
- commonly due to bacterial/viral co-infection

### Predisposing Factors
- Eustachian tube dysfunction/obstruction
  - swelling of tubal mucosa
    - upper respiratory tract infection (URTI)
    - allergic rhinitis
    - chronic rhinosinusitis
  - obstruction/infiltration of Eustachian tube ostium
    - tumour: nasopharyngeal carcinoma (adults)
    - adenoid hypertrophy (by maintaining a source of infection rather than obstruction)
    - barotrauma (sudden changes in air pressure)
  - inadequate tensor palati function: cleft palate (even after repair)
  - abnormal Eustachian tube
    - Down syndrome (horizontal position of Eustachian tube), Crouzon syndrome, cleft palate, and Apert syndrome
- disruption of action of:
  - cilia of Eustachian tube: Kartagener's syndrome
  - mucus secreting cells
  - capillary network that provides humoral factors, PMNs, phagocytic cells
- immunosuppression/deficiency due to chemotherapy, steroids, DM, hypogammaglobulinemia, cystic fibrosis

### Risk Factors
- non-modifiable: young age, family history of OM, prematurity, orofacial abnormalities, immunodeficiencies, Down syndrome, race, and ethnicity
- modifiable: lack of breastfeeding, daycare attendance, household crowding, exposure to cigarette smoke or air pollution, pacifier use

### Pathogenesis
- obstruction of Eustachian tube → air absorbed in middle ear → negative pressure (an irritant to middle ear mucosa) → edema of mucosa with exudate/effusion → infection of exudate from nasopharyngeal secretions

### Clinical Features
- triad of otalgia, fever (especially in younger children), and conductive hearing loss
- rarely tinnitus, vertigo, and/or facial nerve paralysis
- otorrhea if tympanic membrane perforated
- infants/toddlers
  - ear-tugging (this alone is not a good indicator of pathology)
  - hearing loss, balance disturbances (rare)
  - irritable, poor sleeping
  - vomiting and diarrhea
  - anorexia
- otoscopy of TM
  - hyperemia
  - bulging, pus may be seen behind TM
  - loss of landmarks: handle and long process of malleus not visible



**Clinical Assessment of AOM in Pediatrics**
JAMA 2010;304:2161-69
In assessment of AOM in pediatrics, ear pain is the most useful symptom with a likelihood ratio (LR) between 3.0-7.3. Useful otoscopic signs include erythematous (LR 8.4, 95% CI 7-11), cloudy (LR 34, 95% CI 28-42), bulging (LR 51, 95% CI 36-73), and immobile tympanic membrane (LR 31, 95% CI 26-37) on pneumatic otoscopy.

### Diagnosis
- history
  - acute onset of otalgia or ear tugging in a preverbal child, otorrhea, decreased hearing
  - unexplained irritability, fever, upper respiratory symptoms, poor sleeping, anorexia, N/V, and diarrhea
- physical
  - febrile
  - MEE on otoscopy: immobile tympanic membrane, acute otorrhea, loss of bony landmarks, opacification of TM, air-fluid level behind TM
  - MEI on otoscopy: bulging TM with marked discolouration (hemorrhagic, red, grey, or yellow)

### Management
- supportive care and symptom management: maintain hydration, analgesic, and antipyretic (acetaminophen, ibuprofen)
- watchful waiting: in a generally healthy child >6 mo of age with unilateral, non-severe, suspected AOM
  - without MEE or with MEE but non-bulging or mildly erythematous TM
- consider viral etiology
- reassess in 24-48 h if not clinically improved (or earlier if worsening)
  - mildly ill (alert, responsive, no rigors, mild otalgia, fever <39 °C, <48 h illness) with MEE present AND bulging TM
- recommend analgesia
- observe and follow-up in 24-48 h – if not improved or worsening, treat with antimicrobials
- antimicrobial indications: infants <6 mo of age or in a generally healthy child >6 mo of age with suspected AOM and the following features
  - moderately or severely ill (irritable, difficulty sleeping, poor antipyretic response, severe otalgia) OR fever ≥39 °C OR >48 h of symptoms
    - treat with antimicrobials: 10 d course if 6-24 mo, 5 d if ≥2 yr old
  - perforated TM with purulent drainage
    - treat with antimicrobials for 10 d
- referral to otolaryngology for myringotomy and tympanostomy tubes may be warranted for recurrent infections

### Treatment
- antimicrobial agents for AOM
  - 5 d course of appropriate dose antimicrobial recommended for most ≥ 2 yr old with uncomplicated AOM. 10 d course for 6-24 mo, perforated TM, or recurrent AOM
  - 1st line treatment (no penicillin allergy)
- amoxicillin: 5 d course of 45-60 mg/kg/d divided 3x/d, or 75-90 mg/kg/d divided 2x/d
  - 2nd line treatment
    - cefprozil: 30 mg/kg/d divided 2x/d
    - cefuroxime axetil: 30 mg/kg/d divided 2-3x/d (1st line for penicillin allergy)
    - ceftriaxone: 50 mg/kg IM (or IV) x 3 doses (1st line for penicillin allergy)
    - azithromycin: 10 mg/kg OD x 1 dose, then 5 mg/kg OD x 4 doses
    - clarithromycin: 15 mg/kg/d divided 2x/d
  - if initial therapy fails (i.e. no symptomatic improvement after 2-3 d)
    - amoxicillin-clavulanate: 45-60 mg/kg/d (7:1 formulation, 400 mg/5 mL suspension) for 10 d for child weighing ≤35 kg, or 500 mg tablets tid for 10 d for child weighing >35 kg
    - if AOM-related symptoms do not resolve with amoxicillin/clavulanate, a course of ceftriaxone 50 mg/kg/d IM (or IV) OD x 3 doses could be considered

### Complications
- extracranial
  - hearing loss and speech delay (secondary to persistent MEE), TM perforation, extension of suppurative process to adjacent structures (mastoiditis, petrositis, labyrinthitis), cholesteatoma, facial nerve palsy, middle ear atelectasis, ossicular necrosis, vestibular dysfunction, persistent effusion (often leading to hearing loss)
- intracranial
  - meningitis, epidural/brain abscess, subdural empyema, lateral and cavernous sinus thrombosis, carotid artery thrombosis, facial nerve paralysis
- other
  - mastoiditis, labyrinthitis, sigmoid sinus thrombophlebitis

**Antibiotics for Acute Otitis Media in Children**
Cochrane DB Syst Rev 2013;1:CD000219
**Study**: Meta-analysis of Randomized Controlled Trials (RCTs) on children (1-15 mo) with acute otitis media comparing any antibiotic regime to placebo and expectant observation.
**Data Sources**: Cochrane Central Register of Controlled Trials (2012 issue 10), MEDLINE (1966 to October 2012), OLDMEDLINE (1958 to 1965), EMBASE (January 1990 to November 2012), Current Contents (1966 to November 2012), CINAHL (2008 to November 2012) and LILACS (2008 to November 2012) without language restrictions.
**Main Outcomes**: 1) Pain at 24 h, 2-3 d, and 4-7 d; 2) Abnormal tympanometry findings; 3) TM perforation; 4) Contralateral otitis; 5) AOM recurrences; 6) Serious complications from AOM; 7) Adverse effects from antibiotics.
**Results**: Treatment with antibiotics had no significant impact on pain at 24 h. However, pain at 2-3 d and 4-7 d was lower in the antibiotic groups with a NNT of 20. Antibiotics had no significant effect on tympanometry findings, number of AOM recurrences, or severity of complications. Antibiotic treatment led to a significant reduction in TM perforations (NNT 33) and halved contralateral AOM (NNT 11). Adverse events (vomiting, diarrhea, or rash) occurred more often in children taking antibiotics.
**Conclusion**: The role of antibiotics is largely restricted to pain control at 2-7 d, but most (82%) settle without antibiotics. This can also be achieved by analgesics. However, antibiotic treatment can reduce risk of TM perforation and contralateral AOM episodes. These benefits must be weighed against risks of adverse events from antibiotics.

## Otitis Media with Effusion

### Definition
- presence of fluid in the middle ear without signs or symptoms of ear infection

### Epidemiology
- most common cause of pediatric hearing loss
- not exclusively a pediatric disease
- frequently follows AOM in children
- middle ear effusions have been shown to persist following an episode of AOM for 1 mo in 40% of children, 2 mo in 20%, and >3 mo in 10% (i.e. 90% of children clear the fluid within 3 mo – observe for 3 mo before considering myringotomy and tubes)

### Risk Factors
- same as AOM

### Clinical Features
- conductive hearing loss ± tinnitus
  - confirm with audiogram and tympanogram (flat) (see Figure 16B, OT10 and Figure 17B, OT11)
- fullness – blocked ear
- ± pain, low grade fever
- otoscopy of tympanic membrane
  - discolouration – amber or dull grey with "glue" ear
  - meniscus fluid level behind TM
  - air bubbles
  - retraction pockets/TM atelectasis
  - most reliable finding with pneumatic otoscopy is immobility with pneumatic otoscopy

### Treatment
- expectant: 90% resolve by 3 mo
  - watchful waiting for 3 mo from onset, or 3 mo from diagnosis if onset unknown
- document hearing loss with audiogram
- no clinical evidence that antihistamines, decongestants, or antibiotics clear disease faster
- recommend **against** intranasal or systemic steroids, systemic antibiotics, antihistamines, decongestants for OME treatment
- surgery: myringotomy ± ventilation tubes to equalize pressure and drain ear (tympanostomy tubes recommended) ± adenoidectomy (not recommended in <4 yr old unless nasal obstruction, chronic adenoiditis; recommended in ≥ 4 yr old)

### Complications of Otitis Media with Effusion
- hearing loss, speech delay, learning problems in young children
- chronic mastoiditis
- ossicular erosion
- cholesteatoma, especially when retraction pockets involve pars flaccida
- retraction of tympanic membrane, atelectasis, ossicular fixation

**Indications for Myringotomy and Tympanostomy Tubes in Recurrent AOM (RAOM) and OME***
- Chronic bilateral OME and documented hearing difficulties >3 mo
- Unilateral or bilateral OME >3 mo and symptoms likely attributable to OME (e.g. balance problems, poor school performance, ear discomfort, etc.)
- At-risk children (permanent hearing loss, speech/language delay, autism-spectrum disorder, craniofacial disorders, blindness, cleft palate, developmental delay) with unilateral or bilateral OME with type B tympanogram or persistent effusion >3 mo
- RAOM (>3 episodes in 6 mo or >4 in 12 mo) with unilateral or bilateral middle ear effusion

*Clinical practice guidelines: Tympanostomy tubes in children. Otolaryng Head Neck 2013;149:S1-S35

**Effectiveness of Tympanostomy Tubes for Otitis Media: A Meta-analysis**
Pediatrics 2017;139(6):e20170125
**Study**: Systematic review evaluating the effectiveness of tympanostomy tubes in children with chronic OM with effusion and recurrent AOM compared to watchful waiting.
**Data Sources**: MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, CINAHL.
**Results**: Children treated with tympanostomy tubes compared with watchful waiting had a net decrease (improvement) in mean hearing threshold of 9.1 dB at 1-3 mo and 0.0 by 12-24 mo. Children with recurrent AOM may have fewer episodes after tympanostomy tube.
**Conclusions**: Tympanostomy tubes improve hearing at 1-3 mo compared with watchful waiting, with no evidence of benefit by 12-24 mo. More evidence is needed for recurrent AOM. The benefits of tympanostomy tubes must be weighed against a variety of associated adverse events.

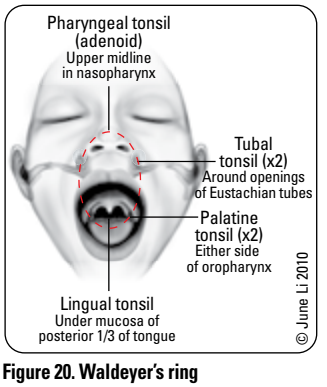



**Figure 20. Waldeyer's ring**
An interrupted circle of protective lymphoid tissue at the upper ends of the respiratory and alimentary tracts

## Adenoid Hypertrophy

### Definition
- size peaks at age 5 and resolves by age 12
- increase in size with repeated URTI and allergies

### Clinical Features
- nasal obstruction
  - adenoid facies (open mouth, high arched palate, narrow midface, malocclusion)
  - history of hypernasal voice and snoring
  - long-term mouth breather; minimal air escape through nose
- choanal obstruction
  - chronic rhinosinusitis/rhinitis
  - obstructive sleep apnea
- chronic inflammation
  - nasal discharge, post-nasal drip, and cough
  - cervical lymphadenopathy

### Diagnosis
- enlarged adenoids on nasopharyngeal exam (usually with flexible nasopharyngoscope)
- enlarged adenoid shadow on lateral soft tissue X-ray

### Complications
- Eustachian tube obstruction leading to serous otitis media
- interference with nasal breathing, necessitating mouth-breathing
- malocclusion
- sleep apnea/respiratory disturbance
- orofacial developmental abnormalities

## Adenoidectomy

### Indications for Adenoidectomy
- chronic upper airway obstruction with sleep disturbance/apnea ± cor pulmonale
- chronic nasopharyngitis resistant to medical treatment
- chronic serous otitis media and chronic suppurative otitis media (with 2nd set of tubes)
- recurrent acute otitis media resistant to antibiotics
- suspicion of nasopharyngeal malignancy
- persistent rhinorrhea secondary to nasal obstruction

### Contraindications
- uncontrollable coagulopathy
- recent pharyngeal infection
- conditions that predispose to velopharyngeal insufficiency (cleft palate, impaired palatal function, or enlarged pharynx)

### Complications
- bleeding, infection
- velopharyngeal insufficiency (hypernasal voice or nasal regurgitation)
- scarring of Eustachian tube orifice

## Sleep-Disordered Breathing in Children

### Definition
- spectrum of sleep-related breathing abnormalities ranging from snoring to OSA

### Epidemiology
- peak incidence between 2-8 yr when tonsils and adenoids are the largest relative to the pharyngeal airway

### Etiology
- due to a combination of anatomic and neuromuscular factors
  - adenotonsillar hypertrophy
  - craniofacial abnormalities
  - neuromuscular hypotonia (e.g. cerebral palsy, Down syndrome)
  - obesity

### Clinical Features
- heavy snoring, mouth breathing, pauses or apnea, enuresis, excessive daytime sleepiness, behavioural/learning problems, diagnosis of ADHD, morning headache, failure to thrive, sleeping with neck hyperextended, cyanosis

### Investigations
- flexible nasopharyngoscopy for assessment of nasopharynx and adenoids
- polysomnography (apnea-hypopnea index >1/h considered abnormal)
  - children: Mild OSA ≥1 to <5/h; Moderate OSA ≥5 to <10/h; Severe OSA ≥10/h
  - adults: Mild OSA 5.1-15/h; Moderate OSA 15.1-30/h; Severe OSA >30.1/h

### Treatment
- nonsurgical: CPAP, BiPAP, sleep hygiene, weight loss in overweight/obese child with OSA
- medication: topical nasal steroids and leukotriene-receptor antagonists for mild OSA or residual sleep-disordered breathing post-adenotonsillectomy
- surgical: bilateral tonsillectomy and adenoidectomy is first surgery of choice
  - if persistent obstructive sleep apnea following tonsillectomy and adenoidectomy, consider adenoid regrowth
  - if these fail and not tolerant of positive airway pressure (PAP) therapy, consider lingual tonsillectomy, midline glossectomy, or other surgeries targeting areas of resistance as required (STAR surgery); surgery may be guided by Drug-Induced Sleep Endoscopy (DISE) or cineradiography-MRI to localize site of resistance

## Acute Tonsillitis

- see Pediatrics, P55

## Peritonsillar Abscess (Quinsy)



**Quinsy Triad**
- Trismus
- Uvular deviation
- Dysphonia ("hot potato voice")

### Definition
- cellulitis of space behind tonsillar capsule extending onto soft palate, leading to abscess

### Etiology
- bacterial: group A *Streptococcus* (GAS) (50% of cases), *S. pyogenes, S. aureus, H. influenzae*, and anaerobes

### Epidemiology
- can develop from acute tonsillitis with infection spreading into plane of tonsillar bed
- unilateral
- most common in 15-30 yr age group

### Clinical Features
- trismus (due to irritation and reflex spasm of the medial pterygoid) is the most reliable indicator of peritonsillar abscess
- fever and dehydration
- sore throat, dysphagia, and odynophagia
- extensive peritonsillar swelling but tonsil may appear normal

- edema of soft palate
- uvular deviation
- dysphonia (edema → failure to elevate palate) 2° to CN X involvement
- unilateral referred otalgia
- cervical lymphadenitis

### Complications
- aspiration pneumonia 2° to spontaneous rupture of abscess
- airway obstruction
- lateral dissection into parapharyngeal and/or carotid space
- bacteremia
- retropharyngeal abscess

### Treatment
- secure airway
- surgical drainage (incision or needle aspiration) with C&S
- warm saline irrigation
- IV penicillin G x 10 d if cultures positive for GAS
- add PO/IV metronidazole or clindamycin x 10 d if culture positive for *Bacteroides*
- consider tonsillectomy after second episode

### Other Sources of Parapharyngeal Space Infections
- pharyngitis
- acute suppurative parotitis (see *Salivary Glands*, OT30)
- AOM
- mastoiditis (Bezold's abscess)
- odontogenic infection

## Tonsillectomy

### Absolute Indications
- most common indication: sleep-disordered breathing
- 2nd most common indication: recurrent throat infections
- tonsillar hypertrophy causing upper airway obstruction, obstructive sleep apnea, severe dysphagia, or cardiopulmonary complications such as cor pulmonale
- suspicion of malignancy (e.g. lymphoma, squamous cell carcinoma)
- orofacial/dental deformity
- hemorrhagic tonsillitis

### Relative Indications (To Reduce Disease Burden)
- recurrent throat infection with a frequency of at least 7 episodes in the past year, at least 5 episodes per year for 2 yr, or at least 3 episodes per year for 3 yr with documentation in the medical record for each episode of sore throat, and 1 or more of the following: temperature >38.3 °C, cervical adenopathy, tonsillar exudate, or positive test for group A β-hemolytic *Streptococcus* (Paradise Criteria)
- chronic tonsillitis with halitosis (bad breath) or sore throat ± tonsilloliths (clusters of material that form in the crevices of the tonsils)
- complications of tonsillitis: quinsy/peritonsillar abscess, parapharyngeal abscess, retropharyngeal abscess
- failure to thrive

### Relative Contraindications
- velopharyngeal insufficiency: overt or submucous/covert cleft of palate, impaired palatal function due to neurological or neuromuscular abnormalities
- hematologic: coagulopathy, anemia
- infectious: active local infection without urgent obstructive symptoms

### Complications
- hemorrhage: primary (within 24 h); secondary (within first 7-10 d)
- odynophagia and/or otalgia; dehydration 2° to odynophagia
- infection
- atlantoaxial subluxation (Grisel's syndrome) - rare

## Airway Problems in Children

### DIFFERENTIAL DIAGNOSIS BY AGE GROUP

### Neonates (Obligate Nose Breathers)
- extralaryngeal
  - choanal atresia (e.g. CHARGE syndrome)
  - nasopharyngeal dermoid, glioma, encephalocele
  - glossoptosis: Pierre-Robin sequence, Down syndrome, lymphatic malformation, hemangioma

- laryngeal
  - laryngomalacia: most common cause of stridor in children
  - vocal cord palsy (due to trauma or Arnold-Chiari malformation)
  - glottic web
  - subglottic stenosis
  - laryngeal cleft
  - laryngocele
- tracheal
  - tracheoesophageal fistula
  - tracheomalacia
  - vascular rings
  - complete tracheal rings

### 2-3 Months
- congenital
  - laryngomalacia
  - vascular: subglottic hemangioma (more common), innominate artery compression, double aortic arch
  - laryngeal papilloma
- acquired
  - subglottic stenosis: post-intubation
  - tracheal granulation: post-intubation
  - tracheomalacia: post-tracheotomy and TEF repair

### Infants – Sudden Onset
- foreign body aspiration
- croup
- bacterial tracheitis
- caustic ingestion
- epiglottitis

### Children and Adults
- infection
  - Ludwig's angina
  - peritonsillar/parapharyngeal abscess
  - retropharyngeal abscess
- neoplastic
  - squamous cell carcinoma (larynx, hypopharynx (adults))
  - retropharyngeal: lymphoma, neuroblastoma
  - nasopharyngeal: carcinoma, rhabdomyosarcoma
- allergic
  - angioneurotic edema
  - polyps (suspect cystic fibrosis in children)
- trauma
  - laryngeal fracture, facial fracture
  - burns and lacerations
  - post-intubation
  - caustic ingestion
- congenital
  - lingual thyroglossal duct cyst
  - lingual tonsil hypertrophy
  - lingual thyroid

## Signs of Airway Obstruction

### Stridor
- note quality, timing (inspiratory or expiratory)
- body position important
  - lying prone: double aortic arch
  - lying supine: laryngomalacia, glossoptosis
- site of stenosis
  - vocal cords or above: inspiratory stridor
  - subglottis and extrathoracic trachea: biphasic stridor
  - distal tracheobronchial tree: expiratory stridor

### Respiratory Distress
- nasal flaring
- supraclavicular and intercostal indrawing
- sternal retractions
- use of accessory muscles of respiration
- tachypnea
- cyanosis
- altered LOC

### Feeding Difficulty and Aspiration
- supraglottic lesion
- laryngomalacia
- vocal cord paralysis
- laryngeal cleft → aspiration pneumonia
- TEF

## Acute Laryngotracheobronchitis (Croup)

### Definition
- inflammation of tissues in subglottic space ± tracheobronchial tree
- swelling of mucosal lining associated with thick, viscous, mucopurulent exudate which compromises upper airway (subglottic space is narrowest portion of upper airway)
- normal function of ciliated mucous membrane impaired

### Etiology
- viral: parainfluenzae I (most common), II, III, influenza A B, RSV

### Clinical Features
- age: 4 mo-5 yr
- preceded by URTI symptoms
- generally occurs at night
- biphasic stridor and croupy cough (loud, sea-lion bark)
- appear less toxic than epiglottitis
- supraglottic area normal
- rule out foreign body and subglottic stenosis
- "steeple-sign" on AP X-ray of neck
- if recurrent croup, think subglottic stenosis

**Signs of Croup**

**The 3 Ss**
**S**tridor
**S**ubglottic swelling
**S**eal bark cough

### Treatment
- racemic epinephrine via metred-dose inhaler q1-2h prn (only if in respiratory distress)
- systemic corticosteroids (e.g. dexamethasone 0.5 mg/kg, prednisone)
- adequate hydration
- close observation for 3-4 h
- intubation if severe (use smaller endotracheal tube than expected for age)
- hospitalize if poor response to steroids after 4 h and persistent stridor at rest
- consider alternate diagnosis if poor response to therapy (e.g. bacterial tracheitis)
- if recurrent episodes of croup-like symptoms, perform high kV croup series X-ray (AP and lat) when well to rule out underlying subglottic stenosis and consider bronchoscopy for definitive diagnosis

## Acute Epiglottitis

Acute epiglottitis is a medical emergency

### Definition
- acute inflammation causing swelling of supraglottic structures of the larynx without involvement of vocal cords

### Etiology
- *H. influenzae* type b
- relatively uncommon condition due to HiB vaccine
- common causes now include *S. pneumoniae* and *S. aureus*

### Clinical Features
- any age, most commonly 1-4 yr
- rapid onset
- toxic-looking, fever, anorexia, restlessness
- cyanotic/pale, inspiratory stridor, slow breathing, lungs clear with decreased air entry
- prefers sitting up ("tripod" posture), open mouth, drooling, tongue protruding, sore throat, dysphagia

When managing epiglottitis, it is important not to agitate the child, as this may precipitate complete obstruction

### Investigations and Management
- examining the throat may lead to potential laryngospasm and airway compromise. Ensure an anesthesiologist/otolaryngologist is present and make preparations for intubation or tracheotomy prior to any manipulation
- WBC (elevated), blood and pharyngeal cultures after intubation
- lateral neck radiograph (only done if patient stable)

**Thumb sign:** cherry-shaped epiglottic swelling seen on lateral neck radiograph

### Treatment
- secure airway
- IV access with hydration
- antibiotics: IV cefuroxime, cefotaxime, or ceftriaxone
- moist air
- extubate when leak around tube occurs and afebrile
- watch for meningitis

# Subglottic Stenosis

### Congenital
- diameter of subglottis <4 mm in neonate (due to thickening of soft tissue of subglottic space or maldevelopment of cricoid cartilage)

### Acquired
- following prolonged, repeated, or traumatic intubation
  - most commonly due to endotracheal intubation; nasal intubation is less traumatic and preferred in long-term intubation, as it puts less pressure on the subglottis (tube sits at different orientation) and there is less movement
  - subglottic stenosis is related to duration of intubation and pressure of the endotracheal tube cuff
- can also be due to foreign body, infection (e.g. TB, diphtheria, syphilis), or chemical irritation

### Clinical Features
- biphasic stridor
- respiratory distress
- recurrent/prolonged croup

### Diagnosis
- rigid laryngoscopy and bronchoscopy

### Treatment
- if soft stenosis: divide tissue with knife or laser, dilate with balloon ± steroids
- if firm stenosis: laryngotracheoplasty

# Laryngomalacia

### Definition
- short aryepiglottic folds, omega-shaped epiglottis, pendulous mucosa
- caused by indrawing of supraglottis on inspiration, leading to laryngopharyngeal reflux of acid



Laryngomalacia is the most common cause of stridor in infants

### Clinical Features
- high-pitched inspiratory stridor at 1-2 wk
- stridor is constant or intermittent and more pronounced supine and following URTI
- usually mild, but can be associated with cyanosis or feeding difficulties when severe, leading to failure to thrive

### Treatment
- observation ± proton pump inhibitor (to break the acid reflux cycle that leads to edema and worse airway obstruction) is usually sufficient, as symptoms spontaneously subside by 12-18 mo in >90% of cases
- if severe, division of the aryepiglottic folds (supraglottoplasty) provides relief

# Foreign Body

### Ingested
- usually stuck at cricopharyngeus muscle
- coins, toys, batteries (emergency)
- presents with drooling, dysphagia, stridor if very large



Foreign body inhalation is the most common cause of accidental death in children

### Aspirated
- usually stuck at right main bronchus
- peanuts, carrot, apple core, popcorn, balloons
- presentation
  - stridor if lodged in trachea
  - unilateral "asthma" if bronchial, therefore often misdiagnosed as asthma
  - if totally occludes airway: cough, lobar pneumonia, atelectasis, mediastinal shift, pneumothorax, death



Batteries MUST be ruled out as a foreign body (vs. coins) as they are lethal and can erode through the esophagus. Batteries have a halo sign around the rim on AP X-ray and a step deformity on lateral x-ray

### Diagnosis and Treatment
- sudden onset, not necessarily febrile or elevated WBC
- any patient with suspected foreign body should be kept NPO immediately
- older patient: inspiratory-expiratory chest X-ray (if patient is stable)
- younger patient: right and left decubitus chest X-rays. Lack of lung deflation while resting on dependent side suggests foreign body blocking bronchus
- bronchoscopy or esophagoscopy with removal

# Deep Neck Space Infection

## Definition
- most commonly arise from an infection of mandibular teeth, tonsils, parotid gland, deep cervical lymph nodes, middle ear, or the sinuses
- often a rapid onset and may progress to fatal complications

## Etiology
- usually mixed aerobes and anaerobes that represent the flora of the oral cavity, upper respiratory tract, and certain parts of the ears and eyes

## Clinical Features
- sore throat or pain and trismus
- dysphagia and odynophagia
- stridor and dyspnea
- late findings may include dysphonia and hoarseness
- swelling of the face and neck, erythema
- asymmetry of the oropharynx with purulent oral discharge
- lymphadenopathy

## Diagnosis
- lateral cervical view plain radiograph
- CT
- MRI

## Treatment
- secure the airway
- surgical drainage
- maximum doses of IV systemic antimicrobials regimens according to the site of infection



These investigations should be obtained carefully and the surgeon should consider accompanying the patient, as the worst place to lose an airway is during imaging



Ludwig's angina is the prototypical infection of the submandibular and sublingual space

# Common Medications

**Table 21. Antibiotics**

| Generic Name (Brand Name) | Dose | Indications | Notes |
|---|---|---|---|
| amoxicillin (Amoxil®, Amoxi®, Amox®) | Adult: 500 mg PO tid<br>Children: 75-90 mg/kg/d in 2 divided doses | *Streptococcus, Pneumococcus, H. influenzae, Proteus* coverage | May cause rash in patients with infectious mononucleosis |
| piperacillin with tazobactam (Zosyn®) | 3 g PO q6h | Gram-positive and negative aerobes and anaerobes plus *Pseudomonas* coverage | May cause pseudomembranous colitis |
| ciprofloxacin (Cipro®, Ciloxan®) | 500 mg PO bid | *Pseudomonas*, streptococci, MRSA, and most Gram-negative; no anaerobic coverage | Animal studies suggest that systemic quinolones may cause cartilage necrosis in children |
| erythromycin (Erythrocin®, EryPed®, Staticin®, T-Stat®, Erybid®, Novorythro Encap®) | 500 mg PO qid | Alternative to penicillin | Ototoxic |

**Table 22. Otic Drops**

| Generic Name (Brand Name) | Dose | Indications | Notes |
|---|---|---|---|
| ciprofloxacin (Ciprodex®) | 4 gtt in affected ear bid | For otitis externa and complications of otitis media<br>*Pseudomonas*, streptococci, MRSA, and most Gram-negative; no anaerobic coverage | |
| neomycin, polymyxin B sulfate, and hydrocortisone (Cortisporin Otic®) | 5 gtt in affected ear tid | For otitis externa<br>Used for inflammatory conditions which are currently infected or at risk of bacterial infections | May cause hearing loss if placed in inner ear |
| hydrocortisone and acetic acid (VoSol HC®) | 5-10 gtt in affected ear tid | For otitis media | Bactericidal by lowering pH |
| tobramycin and dexamethasone (TobraDex®) | 5-10 gtt in affected ear bid | For chronic suppurative otitis media | Risk of vestibular or cochlear toxicity |

**Table 23. Nasal Sprays**

| Generic Name (Brand Name) | Indications | Notes |
|---|---|---|
| **Steroid** | | |
| flunisolide (Rhinalar®)<br>budesonide (Rhinocort®)<br>triamcinolonoe (Nasacort®)<br>beclomethasone (Beconase®)<br>mometasone furoate, monohydrate (Nasonex®)<br>fluticasone furoate (Avamys®) | Allergic rhinitis<br>Chronic sinusitis | Requires up to 4 wk of consistent use to have effect<br>Long-term use<br>Dries nasal mucosa; may cause minor bleeding<br>Patient should stop if epistaxis<br>May sting<br>Flonase® and Nasonex® not absorbed systemically |
| **Antihistamine** | | |
| levocarbastine (Livostin®) | Allergic rhinitis | Immediate effect<br>Discontinue if no effect by day 3<br>Use during allergy season |
| **Decongestant** | | |
| xylometazoline (Otrivin®)<br>oxymetazoline (Dristan®)<br>phenylephrine (Neosynephrine®) | Acute sinusitis<br>Rhinitis | Careful if patient has hypertension<br>Short-term use (<5 d)<br>If long-term use, can cause decongestant addiction (i.e. rhinitis medicamentosa) |
| **Antibiotic/Decongestant** | | |
| framycetin, gramicidin, phenylephrine (Soframycin®) | Acute sinusitis | |
| **Anticholinergic** | | |
| ipratropium bromide (Atrovent®) | Vasomotor rhinitis | Careful not to spray into eyes as can cause burning or precipitation of narrow angle glaucoma<br>Increased rate of epistaxis when combined with topical nasal steroids |
| **Lubricants** | | |
| saline, NeilMed®, Rhinaris®, Secaris®, Polysporin®, Vaseline® | Dry nasal mucosa | Use prn<br>Rhinaris® and Secaris® may cause stinging |

Source: Dr. MM Carr

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# Pediatrics

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# Acronyms

| | |
|---|---|
| AAP | American Academy of Pediatrics |
| ABG | arterial blood gas |
| ACE | angiotensin converting enzyme |
| ADH | antidiuretic hormone |
| ALL | acute lymphoblastic leukemia |
| ALPS | autoimmune lymphoproliferative syndrome |
| AML | acute myelogenous leukemia |
| ANA | antinuclear antibody |
| AOM | acute otitis media |
| ARB | angiotensin receptor blocker |
| ARBD | alcohol-related birth defects |
| ARND | alcohol-related neurodevelopmental disorder |
| ASD | atrial septal defect |
| ASOT | antistreptolysin-o titre |
| ATN | acute tubular necrosis |
| AVM | arteriovenous malformation |
| BRUE | brief resolved unexplained events |
| CAH | congenital adrenal hyperplasia |
| CAS | Children's Aid Society |
| CF | cystic fibrosis |
| CHD | congenital heart defect |
| CML | chronic myelogenous leukemia |
| CMV | cytomegalovirus |
| CP | cerebral palsy |
| CPAP | continuous positive airway pressure |
| CPS | Canadian Pediatric Society |
| DAT | direct antiglobulin test |
| DDAVP | 1-desamino-8-D-arginine vasopressin |
| DI | diabetes insipidus |
| DIC | disseminated intravascular coagulation |
| DKA | diabetic ketoacidosis |
| DMARD | disease modifying antirheumatic drug |
| DS | Down syndrome |
| DSD | disorder of sexual differentiation |
| EBV | Epstein-Barr virus |
| Echo | echocardiogram |
| EEG | electroencephalogram |
| EMG | electromyography |
| FAS | fetal alcohol syndrome |
| FASD | fetal alcohol spectrum disorder |
| FISH | fluorescent in situ hybridization |
| FSH | follicle stimulating hormone |
| FTT | failure to thrive |
| G6PD | glucose-6-phosphate dehydrogenase |
| GA | gestational age |
| GBM | glomerular basement membrane |
| GBS | group B Streptococcus |
| GERD | gastroesophageal reflux disease |
| GH | growth hormone |
| GN | glomerulonephritis |
| GSD | glycogen storage disease |
| HBsAg | hepatitis B surface antigen |
| HDNB | hemorrhagic disease of the newborn |
| Hib | Haemophilus influenzae type b |
| HIDA | hepatobiliary iminodiacetic acid |
| HIE | hypoxic ischemic encephalopathy |
| HIV | human immunodeficiency virus |
| HPA | human platelet antigen |
| HRV | human rotavirus |
| HSP | Henoch-Schönlein purpura |
| HUS | hemolytic uremic syndrome |
| IBW | ideal body weight |
| ICH | intracranial hemorrhage |
| ITP | immune thrombocytopenic purpura |
| IUGR | intra-uterine growth restriction |
| IVH | intraventricular hemorrhage |
| IVIg | intravenous immunoglobulin |
| JIA | juvenile idiopathic arthritis |
| LAH | left atrial hypertrophy |
| LBW | low birth weight |
| LGA | large for gestational age |
| LH | luteinizing hormone |
| LLSB | lower left sternal border |
| LMN | lower motor neuron |
| LOC | level of consciousness |
| LP | lumbar puncture |
| LRTI | lower respiratory tract infection |
| LVH | left ventricular hypertrophy |
| MAS | meconium aspiration syndrome |
| MCAD | medium-chain acyl-CoA dehydrogenase |
| MCD | minimal change disease |
| MDI | metred dose inhaler |
| MSUD | maple syrup urine disease |
| NCS | nerve conduction study |
| NEC | necrotizing enterocolitis |
| NF | neurofibromatosis |
| NICU | neonatal intensive care unit |
| NS | normal saline |
| N/V | nausea/vomiting |
| OCP | oral contraceptive pill |
| ORT | oral rehydration therapy |
| OSA | obstructive sleep apnea |
| PAC | premature atrial contraction |
| PDA | patent ductus arteriosus |
| PKU | phenylketonuria |
| PPHN | persistent pulmonary hypertension of newborn |
| PPV | positive pressure ventilation |
| PUVA | psoralen + UVA |
| RAD | right axis deviation |
| RAS | renal artery stenosis |
| RBBB | right bundle branch block |
| RDS | respiratory distress syndrome |
| RF | rheumatoid factor |
| Rh | Rhesus factor |
| RL | Ringer's lactate |
| RSV | respiratory syncytial virus |
| RUSB | right upper sternal border |
| RVH | right ventricular hypertrophy |
| RVOTO | right ventricular outflow tract obstruction |
| SEM | systolic ejection murmur |
| SGA | small for gestational age |
| SIADH | syndrome of inappropriate antidiuretic hormone |
| SIDS | sudden infant death syndrome |
| SVT | supraventricular tachycardia |
| TEF | tracheo-esophageal fistula |
| TM | tympanic membrane |
| TPN | total parenteral nutrition |
| TTN | transient tachypnea of the newborn |
| UMN | upper motor neuron |
| URTI | upper respiratory tract infection |
| UVA | ultraviolet A |
| VCUG | voiding cystourethrogram |
| VSD | ventricular septal defect |
| VUR | vesicoureteral reflux |
| WPW | Wolff-Parkinson-White |

# Pediatric Quick Reference Values

**Table 1. Average Vitals at Various Ages**

| Age (years) | Pulse (bpm) | Respiratory Rate (br/min) | sBP (mmHg) |
|---|---|---|---|
| <1 | 110-160 | 30-40 | 70-90 |
| 1-2 | 100-150 | 25-35 | 80-95 |
| 2-5 | 95-140 | 25-35 | 80-100 |
| 5-12 | 80-120 | 20-25 | 90-110 |
| >12 | 60-100 | 15-20 | 110-120 |

# Primary Care

## Visit Overview

- schedule
  - newborn (within 1 wk post-discharge), 1, 2, 4, 6, 9, 12, 15, 18, 24 mo
  - annually between age 2-5; every 1-2 yr between age 6-18
- content
  - history and physical exam including growth, development, and nutrition
  - routine immunizations
  - counselling and anticipatory guidance
  - see evidence based clinical tools such as Rourke baby record and Greig health record for more information

### Standard Pediatric History

- acronym: **BINDS**: **B**irth, **I**mmunization, **N**utritional, **D**evelopmental, **S**ocial
- ID: name, age, major chronic medical concerns
- CC/RFR (chief complaint/reason for referral):
- HPI:
  - OPQRSTU
  - recent travel, sick contacts
- obstetrical history
  - prenatal/pregnancy history
    - conception
    - screening: blood group, Rh, DAT, HBsAg, Rubella, Syphilis, HIV, GBS

        - genetic screening: MSS, FTS, IPS, amniocentesis, special tests
        - ultrasounds
        - complications: illnesses, infections, bleeding, gestational diabetes (GDM), gestational hypertension (GHTN),
        - medications, vitamins, iron, smoking, drinking, drug use
        - gestational age at birth, birth weight
    - labour and delivery or birth history
        - labour complications: prolonged rupture of membranes, maternal fever, fetal tachycardia, meconium
        - spontaneous vaginal delivery, interventions required: forceps, vacuum, caesarian section (C/S)
        - resuscitation: APGARs
- past medical history
    - hospitalizations
    - past surgeries
- medications
- allergies
- immunizations
- developmental history
    - meeting major milestones
    - behavioural concerns
- nutritional history
    - breast vs formula feeding
    - milk intake
    - solids, variety etc
- family history
    - consanguinity
- social history
    - Who lives at home? Siblings?
    - Does the child attend daycare? Primary care givers?
    - school adjustment, friends, activities, safety, stability, stressors
    - HEADDSS history for adolescents

# Routine Immunization

**Table 2. Publicly Funded Immunization Schedule for Ontario, December 2016**

| Age | DTaP-IPV-Hib | TdaP-IPV | Pneu-C-13 | Rot-1 | Men-C-C | MMR | Var | MMRV | Men-C-ACYW | HepB | HPV-4 | Tdap | Inf |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 mo | ✓IM | | ✓IM | ✓PO | | | | | | | | | |
| 4 mo | ✓IM | | ✓IM | ✓PO | | | | | | | | | |
| 6 mo | ✓IM | | | | | | | | | | | | |
| 12 mo | | | ✓IM | | ✓IM | ✓SC | | | | | | | |
| 15 mo | | | | | | | ✓SC | | | | | | |
| 18 mo | ✓IM | | | | | | | | | | | | |
| 4-6 yr* | | ✓IM | | | | | | ✓SC | | | | | |
| Grade 7 | | | | | | | | | ✓IM | ✓IM 3 doses (0,1,6 mo) | ✓IM 2 doses (0,6 mo) | | |
| 14-16 yr | | | | | | | | | | | | ✓IM | |
| Every autumn (beginning at age 6 mo) | | | | | | | | | | | | | ✓IM |

IM = intramuscular; PO = per oral; SC = subcutaneous  * Preferably given at 4 years of age
DTaP = diphtheria, tetanus, acellular pertussis vaccine; TdaP-IPV = diphtheria, tetanus, acellular pertussis, inactivated polio vaccine (i.e. Pentacel®, Pentavax®);
HepB = hepatitis B vaccine; Hib = *Haemophilus influenzae* type b conjugate vaccine; HPV-4 = human papillomavirus vaccine; Inf = influenza vaccine;
MMR = measles, mumps, rubella vaccine; Men-B = multicomponent meningococcal B vaccine; Men-C-C = meningococcal c conjugate vaccine; Men ACYW – meningococcal vaccine; MMRV = measles, mumps, rubella, varicella vaccine; Pneu-C-13 = pneumococcal 13-valent conjugate vaccine; Rot-1 = rotavirus oral vaccine; Var = varicella vaccine

**Table 3. Adverse Reactions and Contraindications of Routine Immunizations**

| Vaccine | Adverse Reaction | Contraindication |
|---|---|---|
| TdaP-IPV | Prolonged crying<br>Hypotonic unresponsive state (rare)<br>Seizure on day of vaccine (rare) | Evolving unstable neurologic disease<br>Hyporesponsive/hypotonic following previous vaccine<br>Anaphylactic reaction to neomycin or streptomycin |
| Rot-1 | Cough<br>Diarrhea, vomiting | History of intussusception<br>Immunocompromised<br>Abdominal disorder (e.g. Meckel's diverticulum)<br>Received blood products (e.g. immunoglobulin) within 42 d |
| MMR | Measle-like rash (7-14 d)<br>Lymphadenopathy, arthralgia, arthritis<br>Parotitis (rare)<br>Especially painful injection<br>Transient thrombocytopenia (1/30,000) | Pregnancy<br>Immunocompromised infants (except healthy HIV positive children)<br>Anaphylactic reaction to gelatin |

**Canadian Immunization Guide**
National Advisory Committee on Immunization. Canadian Immunization Guide (CIG). Last Modified 2014. Public Health Agency of Canada, 2006. Available at: http://www.phac-aspc.gc.ca/publicat/cig-gci/

According to the CDC, the weight of currently available scientific evidence does not support the hypothesis that MMR vaccine causes either autism or IBD. The landmark paper linking autism to the MMR vaccine (*Lancet* 1998;351:637-641) was retracted due to false claims in the article (*Lancet* 2010;375:445)

**Adverse Reactions Associated With Any Vaccine**
- **Local**: induration, tenderness, redness, swelling
- **Systemic**: fever, rash, irritability
- **Allergic**: urticaria, rhinitis, anaphylaxis
- **Contraindications**
    - Moderate/severe illness ± fever
    - Allergy to vaccine component
- No need to delay vaccination for mild URTI

**Vaccination in Cases of Asplenia or Hyposplenia (such as Sickle Cell Disease)**
- Should receive all routine immunizations, including the yearly influenza vaccine
- No vaccines are contraindicated
- Susceptible to infection by encapsulated bacteria ("SHiNE KISS" –*S. pneumoniae, H. influenzae, N. meningitidis, E. coli, Klebsiella, Salmonella*, Group B Strep), so must add:
- Quadrivalent conjugated Meningococcal C vaccine (Men-C-ACYW) and Meningococcal B vaccine (4CMenB) at time of diagnosis if ≥2 mo (2-3 doses given at least 8 wk apart) with booster at 12-23 mo, every 3-5 yr until 7 yr of age, and every 5 yr thereafter
- Can omit routine Meningococcal-C-Conjugate at 12 mo of age if received Men-C-ACYW and expected to receive a second dose within 8 wk
- Pneumococcal polysaccharide vaccine (Pneu-P-23) at age ≥2 yr and single booster ≥5 yr after first dose
- Consider single booster HiB at age >5 yr

**Injection site**
Infants (<12 mo): anterolateral thigh

**Table 3. Adverse Reactions and Contraindications of Routine Immunizations** (continued)

| Vaccine | Adverse Reaction | Contraindication |
|---|---|---|
| Var | Mild varicella-like papules or vesicles; 2 wk may get local or generalized rash | Pregnant or planning to get pregnant within 3 mo<br>Anaphylactic reaction to gelatin |
| HepB | | Anaphylactic reaction to Baker's yeast |
| MMRV | Same as MMR and Var vaccines | Same as MMR and Var vaccines |
| DTaP | | 1st trimester pregnancy |
| Inf | Malaise, myalgia<br>Febrile seizure when given with Pneu-C 13 or DTaP<br>Hypersensitivity reaction | <6 mo of age<br>Immunocompromised<br>Egg-allergic individuals – Live attenuated influenza vaccine is not recommended for those with an egg allergy. In these individuals, trivalent or quadrivalent vaccine can be given in environment where anaphylaxis can be managed |
| HPV-4 | Pruritis | |
| MenB* | | Anaphylactic reaction to MenB vaccine or its components in the past |

* Currently only publicly funded for select groups (asplenia, antibody/complement deficiencies, cochlear implant recipients, HIV, close contacts with infected individuals)

DTaP = diphtheria, tetanus, acellular pertussis vaccine; TdaP-IPV = diphtheria, tetanus, acellular pertussis, inactivated polio vaccine (i.e. Pentacel®, Pentavax®); HepB = hepatitis B vaccine; Hib = *Haemophilus influenzae* type b conjugate vaccine; HPV-4 = human papillomavirus vaccine; Inf = influenza vaccine; MMR = measles, mumps, rubella vaccine; Men-B = multicomponent meningococcal B vaccine; Men-C-C = meningococcal c conjugate vaccine; Men ACYW – meningococcal vaccine; MMRV = measles, mumps, rubella, varicella vaccine; Pneu-C-13 = pneumococcal 13-valent conjugate vaccine; Rot-1 = rotavirus oral vaccine; Var = varicella vaccine

**Safety and Efficacy of an Attenuated Vaccine Against Severe Rotavirus Gastroenteritis**
NEJM 2006;354:11-22
**Purpose:** To evaluate the safety and efficacy of an attenuated G1P[8] human rotavirus (HRV) vaccine.
**Methods:** Randomized, double-blind, phase 3 trial including healthy infants from Latin America and Finland, assigned to receive two oral doses of HRV vaccine versus placebo at 2 and 4 mo of age. Primary outcomes were episodes of gastroenteritis and severity.
**Results:** 63,225 healthy infants were enrolled. The vaccine was 85% efficacious against severe rotavirus gastroenteritis and hospitalizations associated with gastroenteritis (p<0.001) and 100% efficacious against more severe gastroenteritis. Hospitalization for diarrhea of any cause was reduced by 42% (95% CI 29-53%, p<0.001). Six vaccine recipients and seven placebo recipients had definite intussusception within 31 d after each dose (risk difference -0.32/10,000 infants; 95% CI -2.91 to 2.18, **p=0.78**).
**Conclusion:** Two oral doses of the live attenuated HRV vaccine were highly efficacious in decreasing incidence of severe rotavirus and all-cause gastroenteritis, and were not associated with an increased risk of intussusception.

# Growth and Development

## Growth

- growth is not linear
  - most rapid growth during first 2 yr and at puberty
- measurement of growth
  - premature infants (<37 wk) use corrected GA until age 2
  - body proportion = upper/lower segment ratio (use symphysis pubis as midpoint)
    - newborn = 1.7, adult male = 0.9, adult female = 1.0

## Average Growth Parameters

**Table 4. Parameters of Average Growth at Birth**

| | Normal | Growth | Comments |
|---|---|---|---|
| **Birth Weight** | 3.25 kg (7 lbs) | Gain 20-30 g/d (term neonate)<br>2 x birth wt by 4-5 mo<br>3 x birth wt by 1 yr<br>4 x birth wt by 2 yr | Weight loss (up to 10% of birth weight) in first 7 d of life is normal<br>Neonate should regain birth weight by ~10-14 d of age |
| **Length/Height** | 50 cm (20 in) | 25 cm in 1st yr<br>12 cm in 2nd yr<br>8 cm in 3rd yr then<br>4-7 cm/yr until puberty<br>1/2 adult height at 2 yr | Measure supine length until 2 yr of age, then measure standing height |
| **Head Circumference** | 35 cm (14 in) | 2 cm/mo for 1st 3 mo<br>1 cm/mo at 3-6 mo<br>0.5 cm/mo at 6-12 mo | Measure around occipital, parietal, and frontal prominences to obtain the greatest circumference |

## Reflexes

**Table 5. Developmental or Primitive Reflexes**

| Reflex | Maneuver to Elicit Reflex | Appropriate Reflex Response | Age of Disappearance |
|---|---|---|---|
| **Moro** | Infant placed semi-upright, head supported by examiner's hand, sudden withdrawal of supported head with immediate return of support | Abduction and extension of the arms, opening of the hands, followed by flexion and adduction of arms | 4-6 mo |
| **Galant** | Infant held in ventral suspension and one side of back is stroked along paravertebral line | Pelvis will move in the direction of stimulated side | 2-3 mo |
| **Grasp** | Placement of examiner's finger in infant's palm | Flexion of infant's fingers | 3-4 mo |
| **ATNR** | Turn infant's head to one side | "Fencing" posture (extension of ipsilateral arm and leg and flexion of contralateral arm and leg) | 4-6 mo |
| **Placing** | Dorsal surface of infant's foot placed touching edge of table | Flexion followed by extension of ipsilateral limb up onto table (resembles primitive walking) | variable |
| **Rooting** | Tactile stimulus near mouth | Infant turns head and opens mouth to suck on same side that cheek was stroked | 2-3 mo |
| **Parachute** | Tilt infant to side while in sitting position | Ipsilateral arm extension, present by 6-8 mo | Does not disappear |

ATNR = asymmetric tonic neck reflex

**Abnormal Reflex Response (primitive reflex response present in infancy; tendon reflex response always present)**
- Primitive reflex responses are abnormal if: absent during neonatal period; assymetric; or persistent after 4-6 mo (e.g. cerebral palsy)
- Tendon reflex responses: asymmetry suggests focal motor lesions (e.g. brachial plexus injury); and absence or hyper-reflexia may suggest CNS abnormality
- Upgoing plantar reflex (Babinski's sign) normal in infants up to age 2 yr

## Developmental Milestones

### Table 6. Developmental Milestones

| Age* | Gross Motor | Fine Motor | Speech and Language | Cognitive/Problem Solving | Social/Emotional |
|---|---|---|---|---|---|
| **Newborn** | Primitive reflexes: step, place, Moro, Babinski, asymmetrical tonic neck reflex | Primitive reflexes: grasp | Primitive reflexes: root, suck | Fix and follow slow horizontal arc | Bonding between parent and child |
| **2 mo** | Briefly raises head 45° when prone | Hands open half of time | Turns to voice, cooing | Prefers familiar caregiver | Social smile |
| **4 mo** | Rolls prone to supine | Palmar grasp, reaches and obtains items, brings objects to midline | Squeals, laughs | Purposeful sensory exploration of objects (eyes, hands, mouth) | Explores parent's face |
| **6 mo** | Tripod sit, rolls both ways | Transfers objects from hand to hand | Babbles (nonspecific) | Stranger anxiety | Expresses emotions: happy, sad, mad |
| **9 mo** | Sits well without support, crawls, pulls to stand | Inferior pincer grasp | "Mama, dada" Gestures "bye bye", "up" | Plays games (e.g. peek-a-boo) Object permanence | Separation anxiety |
| **12 mo** | Walks a few steps | Fine pincer (fingertips), finger-feeds cheerios | 1 word with meaning (besides mama, dada), responds to own name, follows 1-step command with gesture | Uses objects functionally, cause and effect | Points at wanted items |
| **15 mo** | Walks without support, crawls up stairs/steps | Stacks 2 blocks, uses spoon | 4-5 words, follows 1-step command without gesture | Looks for moved hidden object if saw it being moved | Shared attention: points at interesting items to show to parent |
| **18 mo** | Runs, stoops and recovers | Tower of 4 blocks, scribbling, fisted pencil grasp | 10-25 words 3 body parts | Symbolic play with doll or bear | Parallel play |
| **24 mo** | Jumps on two feet | Tower of 6 cubes, handedness established | 2-3 word phrases, uses "I, me, you", 50% intelligible, understands 2-step commands | New problem-solving strategies without rehearsal | Testing limits, tantrums |
| **3 yr** | Rides tricycle, climbs up 1 foot per step | Toilet trained, undresses, draws circle and cross (+) | 3-step commands, 3-4 word phrases, "W" questions ("why?"), 200 words, 75% intelligible | Identifies shapes, counts to 3 | Cooperative play, role play (pretend play) |
| **4 yr** | Hops on 1 foot, climbs down 1 foot per step | Uses scissors, buttons clothes | Speech 100% intelligible, uses past tense, tells a story | Identifies 4 colours, counts to 4 | Has a preferred friend |
| **5 yr** | Skips, rides bicycle | Prints name, ties shoelaces | Fluent speech, future tense | Counts to 10 accurately, recite ABC's | Has group of friends |

*Use corrected GA until 2 yr

**Developmental Red Flags**
- Gross motor: not walking at 18 mo rolling too early at <3 mo
- Fine motor: hand preference at <18 mo
- Speech: <10 words at 18 mo
- Social: not smiling at 3 mo; not pointing at 15-18 mo
- See the Nipissing District Developmental Screen for a checklist of important 18 mo milestones: www.ndds.ca

# Nutrition

## Dietary Requirements

| Weight | <10 kg | 10-20 kg | >20 kg |
|---|---|---|---|
| Needs | 100 kcal/kg/d | 1000 cal + 50 kcal/kg/d for each kg >10 | 1500 cal + 20 kcal/kg/d for each kg >20 |

## Dietary Recommendations

- 0-6 mo: breast milk or formula
  - exclusive breast milk during first 6 mo recommended over formula unless contraindicated
  - breastfed infants require supplements: vitamin D (400 IU/d), fluoride (after 6 mo if not sufficient in water), iron (6-12 mo, only if not receiving fortified cereals/meat/meat alternatives)
- >6 mo: solid food introduction – do not delay beyond 9 mo
  - 2-3 new foods per wk, wait at least 2 d in between each food to allow time for adverse reaction identification
    - common allergens: eggs, milk, mustard, peanuts, seafood, sesame, soy, tree nut, wheat
  - early introduction of highly allergenic foods is recommended
  - offer lumpy, soft-cooked, pureed, mashed textured foods
  - 9-24 mo: switch to homogenized (3.25%) milk, offer 16oz/d to non-breast feeding infant
  - offer vegetables, fruit, grains, and full-fat milk in any order after iron-rich foods are given
  - provide up to 3 large feedings (meals) with 1-2 smaller feedings (snacks), depending on child's hunger/satiety cues
  - encourage self-feeding and introduce open cup (should be done by 18 mo)
  - foods to avoid
    - honey until past 12 mo (risk of botulism)

**Peanut Allergies in Children**
NEJM 2015;372(9):803-813
**Study:** 640 children identified as "at risk to peanut allergy" due to severe eczema, egg allergy, or both were split into two cohorts depending on their pre-existing sensitivity to peanut extract on skin-prick test. These two cohorts were randomized to peanut consumption or avoidance up until 60 mo of age.
**Results:** In the cohort with negative skin-prick test at start of study, prevalence of peanut allergy at 60 mo of age was 13.7% in peanut avoidance and 1.9% in the peanut consumption group. In cohort with positive skin-prick test at start of study, prevalence of peanut allergy at 60 mo of age was 35.3% in peanut avoidance and 10.6% in peanut consumption group.
**Conclusion:** Early introduction of peanuts significantly decreased prevalence of peanut allergies in children deemed "at risk to peanut allergy".

**Dietary Exposures and Allergy Prevention in High-Risk Infants**
Paediatr Child Health 2013;18(10):545-549
There is no evidence that restriction of highly allergenic foods is beneficial in the first year of life. Later introduction of peanut, fish, or egg does not prevent, and may increase the risk of developing food allergy. There is also no evidence that dietary restrictions during pregnancy or breastfeeding are protective to the child.

- added sugar, salt
- excessive milk (i.e. no more than 750 mL or 24 oz/d after 1 yr)
- limit juice intake (not nutritious, too much sugar), maximum 4-6 oz (1/2 cup) daily
- anything that is a choking hazard (chunks, round foods like grapes)
- 2-6 yr: switch to 2% milk (500 mL/d)
- can maintain breastfeeding during this time complementary to solids

### Breastfeeding

- content of breast milk
  - colostrum (first few days): clear, rich in nutrients (i.e. high protein, low fat), immunoglobulin
  - mature milk: 70:30 whey:casein ratio, fat from dietary butterfat, carbohydrate from lactose
- advantages
  - easily digested, low renal solute load
  - immunologic
    - reduction of acute illnesses (i.e. diarrhea, respiratory tract illnesses, acute otitis media) and may have longer term benefits
    - contains IgA, macrophages, active lymphocytes, lysozymes, lactoferrin (which inhibits *E. coli* growth in intestine)
    - lower pH promotes growth of *Lactobacillus* in GI tract
  - parent-child bonding
  - economical, convenient
- maternal contraindications
  - chemotherapy, radioactive compounds, or medications known to cross to breast milk
  - HIV/AIDS, active untreated TB, herpes in breast region
  - >0.5 g/kg/d of alcohol or illicit drugs
  - OCPs are not a contraindication to breastfeeding (estrogen may decrease lactation, but is not dangerous to infant)
- if poor weight gain: consider dehydration or FTT and may consider formula supplementation if insufficient milk production or intake
- oral candidiasis (thrush): treat baby with antifungal such as nystatin; can occur in breast or bottle-fed infants

**Medications that Cross into Breast Milk**
- Antimetabolites
- Bromocriptine
- Chloramphenicol
- High dose diazepam
- Ergots
- Gold
- Metronidazole
- Tetracycline
- Lithium
- Cyclophosphamide

**Signs of Inadequate Intake**
- <6 wet diapers/d after first wk
- <7 feeds/d
- Sleepy or lethargic, sleeping throughout the night <6 wk
- Weight loss >10% of birth weight
- Jaundice

**Signs of Adequate Intake**
- 1 wet diaper per/d of age for first wk
- 1-2 black or dark green stools (meconium)/d on Day 1 & 2
- 3+ brown/green/yellow stools/d on Day 3 & 4
- 3+ yellow, seedy stools/d on Day 5+

**Table 7. Common Formulas Compared to Breast Milk**

| Type of Nutrition | Indications | Content (as compared to breast milk) |
|---|---|---|
| **Cow's Milk-Based** (Enfamil®, Similac®) | Prematurity<br>Transition to breastfeeding<br>Contraindication to breastfeeding | Lower whey:casein ratio<br>Plant fats instead of dietary butterfat |
| **Fortified Formula** | Low birth weight<br>Prematurity | Higher calories and vitamins A, C, D, K<br>May only be used in hospital due to risk of fat-soluble vitamin toxicity |
| **Soy Protein** (Isomil®, Prosobee®) | Galactosemia<br>Desire for vegetarian/vegan diet* | Corn syrup solids or sucrose in place of lactose |
| **Partially Hydrolyzed Proteins** (Good Start®) | Delayed gastric emptying<br>Risk of cow's milk protein allergy | Protein is 100% whey with no casein |
| **Protein Hydrolysate** (Nutramigen®, Alimentum®, Pregestimil®, Portagen®) | Malabsorption<br>Food allergy including cow's milk protein allergy | Protein is 100% casein with no whey<br>Corn syrup solids, sucrose, or tapioca starch instead of lactose<br>Expensive |
| **Amino Acid** (Neocate®, PurAmino™) | Food allergy<br>Short gut | Free amino acids (no protein)<br>Corn syrup solids instead of lactose<br>Very expensive |
| **Metabolic** | Inborn errors of metabolism | Various different compositions for children with galactosemia, propionic acidemia, etc. |

* 10-35% of children with cow's milk protein allergy also have reactions to soy-based formula

## Injury Prevention Counselling

- injuries are the leading cause of death in children >1 yr of age
- main causes: motor vehicle crashes, burns, drowning, falls, choking, infanticide

**Table 8. Injury Prevention Counselling**

| 0-6 mo | 6-12 mo | 1-2 yr | 2-5 yr |
|---|---|---|---|
| Do not leave alone on bed, on changing table, or in tub<br>Keep crib rails up<br>Check water temperature before bathing<br>Do not hold hot liquid and infant at the same time<br>Check milk temperature before feeding<br>Appropriate car seats are required before leaving hospital | Install stair barriers<br>Discourage use of walkers<br>Avoid play areas with sharp-edged tables and corners<br>Cover electrical outlets<br>Unplug appliances when not in use<br>Keep small objects, plastic bags, cleaning products, and medications out of reach<br>Supervise during feeding<br>Appropriate car seats | Never leave unattended<br>Keep pot handles turned to back of stove<br>Caution with whole grapes, nuts, raw carrots, hotdogs, etc. due to choking hazard<br>No running while eating<br>Appropriate car seats | Bicycle helmet<br>Never leave unsupervised at home, driveway, or pool<br>Teach bike safety, stranger safety, and street safety<br>Swimming lessons (>4 yr), sunscreen (from 6 mo), fences around pools<br>Appropriate car seats |

Note: This list is not exhaustive. For more details, see Rourke Baby Record (http://www.rourkebabyrecord.ca/pdf/RBR2011Ont_Eng.pdf)

## Circumcision

- elective procedure
  - CPS affirms that circumcision is not medically indicated, and does not recommend routine circumcision for every newborn male
  - often for religious or culture reasons
- benefits: prevention of phimosis and slightly reduced incidence of UTI, STI, balanitis, cancer of the penis
- complications (<1%): local infection, bleeding, urethral injury
- **contraindications**: presence of genital abnormalities (e.g. hypospadias) or known bleeding disorder

**Newborn Male Circumcision**
Pediatr Child Health 2015;20(6):311-20
Canadian Paediatric Society and the American Academy of Pediatrics have both previously indicated that circumcision of newborn males is not a medically indicated procedure. Some evidence has subsequently suggested decreased urinary tract infections and incidence of some sexually transmited infections, including HIV, with circumcision. While such a benefit may be present in some boys and high-risk populations where the procedure may be considered in the context of reduction or treatment, the Canadian Paediatric Society continues to not recommend routine circumcision for every newborn male.

# Common Complaints

## Breath Holding Spells

- **clinical feature**: types
  - cyanotic (more common), usually associated with anger/frustration
  - pallid, usually associated with pain/surprise
- **epidemiology**: 0.1-5% of healthy children 6 mo-4 yr of age, usually start during first year of life
- **etiology**: child is provoked (usually by anger, injury, or fear) → holds breath and becomes silent → spontaneously resolves or loses consciousness
- **management**
  - usually resolves spontaneously and rarely progresses to seizure
  - help child control response to frustration and avoid drawing attention to spell
  - may be associated with iron deficiency anemia, improves with supplemental iron

## Crying/Fussing Child

- common etiologies: functional (e.g. hungry, irritable), colic, trauma, illness
- history
  - description of baseline feeding, sleeping, crying patterns
  - infectious symptoms: fever, tachypnea, rhinorrhea, ill contacts
  - feeding intolerance: gastroesophageal reflux with esophagitis, N/V, diarrhea, constipation
  - trauma
  - recent immunizations (vaccine reaction) or medications (drug reactions), including maternal drugs taken during pregnancy (neonatal withdrawal syndrome) and drugs that may be transferred via breast milk
  - inconsistent history, pattern of numerous emergency department visits, high-risk social situations all raise concern of maltreatment
  - consider broad array of possible underlying causes such as meningitis, sepsis, respiratory distress, constipation, etc.

## Infantile Colic

- **clinical feature**: unexplained paroxysms of irritability and crying for >3 h/d, >3 d/wk for >3 wk in an otherwise healthy, well-fed baby (rule of 3s)
- **epidemiology**: 10% of infants; usual onset 10 d to 3 mo of age with peak at 6-8 wk
- **etiology**: unknown. Theories: alterations in fecal microflora, cow's milk intolerance, GI immaturity or inflammation, poor feeding, maternal smoking
- diagnosis of exclusion after thorough history and physical exam to rule out identifiable causes such as otits media, cow's milk intolerance, GI problem, fracture
- **management**
  - parental relief, rest, and reassurance
  - hold baby, soother, car ride, music, vacuum, check diaper
  - some evidence for probiotics
  - maintain breastfeeding but eliminate allergens (cow's milk protein, eggs, wheat, and nuts) from mother's diet
  - time-limited (2 wk) trial of protein hydrolysate formula (e.g. Nutramigen®)
  - time – all resolve, most in the first 3-6 mo of life, no long-term adverse effects

## Dentition and Caries

### Dentition

- primary dentition (20 teeth)
  - first tooth at 5-9 mo (lower incisor), then 1/mo
  - 6-8 central teeth by 1 yr
  - assessment by dentist 6 mo after eruption of first tooth and certainly by 1 yr of age (Grade B recommendation)
- secondary dentition (32 teeth)
  - first adult tooth is 1st molar at 6 yr, then lower incisors

### Caries
- **early childhood caries**: presence of one or more decayed, missing (due to caries), or filled tooth surfaces in any primary tooth in a preschool-aged child
- **etiology**: multifactorial with biomedical factors (e.g. diet, bacteria, host) and social determinants of health
  - inappropriate feeding practices (e.g. frequent, prolonged bottle feeding, putting to bed with bottle, prolonged breast feeding, and excessive juice consumption) are important factors
- **prevention**
  - no bottle at bedtime, clean teeth after last feed
  - minimize juice and sweetened pacifier
  - clean teeth with soft damp cloth or toothbrush and water
  - water fluoridation
  - ensure every child has a dentist by 1 year of age

## Enuresis

### Definition
- involuntary urinary incontinence by day and/or night in child >5 yr

### General Approach
- should be evaluated if: dysuria; change in colour, odour, or stream; secondary or diurnal; change in gait; or stool incontinence are present

### Primary Nocturnal Enuresis
- **clinical feature**: involuntary loss of urine at night, bladder control has never been attained
- **epidemiology**: boys > girls; 10% of 6 yr olds, 3% of 12 yr olds, 1% of 18 yr olds
- **etiology**: developmental disorder or maturational lag in bladder control while asleep
- **management**
  - time, reassurance (~20% resolve spontaneously each yr), and avoidance of punishment or humiliation to maintain self-esteem
  - behaviour modification (limiting fluids and avoid caffeine-containing food before bedtime, void prior to sleep, ensure access to toilet, take out of diapers)
  - conditioning: "wet" alarm wakes child upon voiding (70% success rate)
  - medications (for children >7 yr, considered second line therapy, may be used for sleepovers/camp): DDAVP oral tablets (similar success rate as "wet" alarm therapy but higher relapse rate), imipramine (Tofranil®) (rarely used, lethal if overdose, SE: cardiac toxicity, anticholinergic effects)

### Secondary Enuresis
- **clinical feature**: involuntary loss of urine at night, develops after child has sustained period of bladder control (>6 mo)
- **etiology**: inorganic regression due to stress or anxiety (e.g. birth of sibling, significant loss, family discord, sexual abuse), secondary to organic disease (UTI, DM, DI, sleep apnea, neurogenic bladder, CP, seizures, pinworms)
- **management**: treat underlying cause

### Diurnal Enuresis
- **clinical feature**: daytime wetting (60-80% also wet at night)
- **etiology**: micturition deferral (holding urine until last minute) due to psychosocial stressor (e.g. shy), structural anomalies (e.g. ectopic ureteral site, neurogenic bladder), UTI, constipation, CNS disorders, DM
- **management**: treat underlying cause, behavioural (scheduled toileting, double voiding, good bowel program, sitting backwards on toilet, charting/incentive system, relaxation/biofeedback), good constipation management, pharmacotherapy



Treatment for primary nocturnal enuresis should not be considered until 7 yr of age due to high rate of spontaneous cure



**Antidiuretic Hormone Regulation in Primary Nocturnal Enuresis**
Arch Dis Child 1995;73(6):508-11
**Purpose**: To evaluate the efficacy of DDAVP for the treatment of primary nocturnal enuresis.
**Methods**: Children with primary nocturnal enuresis were compared with a corresponding control group. Diurnal and nocturnal urine production, ADH secretion, and plasma osmolality were determined.
**Results**: Ten children (mean age 10.5 yr) with primary nocturnal enuresis were compared to a control group of eight patients. No differences in urine production, ADH levels during day and night, or plasma osmolality were found. However, the enuretic children required a markedly greater ADH output (2.87 pg/ml/mmol/kg vs. 0.56 in controls; $p<0.01$).
**Conclusion**: ADH secretion is a function of plasma osmolality. Urine production is not increased at night in individuals with primary nocturnal enuresis because of lower ADH secretion.

## Encopresis

- **clinical feature**: fecal incontinence in a child >4 yr old, at least once per mo for 3 mo
- **prevalence**: 1-1.5% of school-aged children (rare in adolescence); M:F = 6:1 in school-aged children
- **causes**: chronic constipation (retentive encopresis), Hirschsprung disease, hypothyroidism, hypercalcemia, spinal cord lesions, anorectal malformations, bowel obstruction

### Retentive Encopresis
- **definition**: child holds bowel movement, develops constipation, leading to fecal impaction and seepage of soft or liquid stool (overflow incontinence)
- **etiology**
  - physical: painful stooling often secondary to constipation
  - emotional: disturbed parent-child relationship, coercive toilet training, social stressors
- **clinical feature**
  - history
    - crosses legs or stands on toes to resist urge to defecate
    - distressed by symptoms, soiling of clothes
    - toilet training coercive or lacking in motivation
    - may show oppositional behaviour
    - abdominal pain

  - physical exam
    - digital rectal exam or abdo x-ray: large fecal mass in rectal vault
    - anal fissures (result from passage of hard stools)
    - palpable stool in LLQ
- **management**
  - complete clean-out of bowel: PEG 3350 given orally is most effective, enemas and suppositories may be second line therapies, but these are invasive and often less effective
  - maintenance of regular bowel movements (see *Constipation*, P39)
  - assessment and guidance regarding psychosocial stressors
  - behavioural modification
- **complications**: recurrence, toxic megacolon (requires >3-12 mo to treat), bowel perforation

# Toilet Training

- 90% of children attain bowel control before bladder control
- generally, females train earlier than males
- 25% by 2 yr (in North America), 98% by 3 yr have daytime bladder control
- signs of toilet readiness
  - ambulating independently, stable on potty, desire to be independent or to please caregivers (i.e. motivation), sufficient expressive and receptive language skills (2-step command level), can stay dry for several h (large enough bladder), can recognize need to go, able to remove clothing

# Failure to Thrive

- **definition**
  - weight <3rd percentile, falls across two major percentile curves, or <80% of expected weight for height and age
  - inadequate caloric intake most common factor in poor weight gain
  - may have other nutritional deficiencies (e.g. protein, iron, vitamin D)
  - factors affecting physical growth: genetics, intrauterine factors, nutrition, endocrine hormones, chronic infections/diseases, psychosocial factors
- **clinical feature**
  - history
    - nutritional intake
    - current symptoms
    - past illnesses
    - family history: growth, puberty, parental height and weight including mid-parental height
    - psychosocial history
  - physical exam
    - growth parameters, plotted: height, weight, head circumference (if ≤2 yr)
      - <2 yr: height, weight, head circumference
      - ≥2 yr: height, weight, BMI
    - vital signs
    - complete head to toe exam
    - dysmorphic features or evidence of chronic disease
    - upper to lower segment ratio
    - sexual maturity staging
    - signs of maltreatment or neglect
- **investigations** (as indicated by clinical feature)
  - CBC, blood smear, electrolytes, T4, TSH
  - bone age x-ray
  - chromosomes/karyotype
  - chronic illness: chest (CXR, sweat $Cl^-$), cardiac (CXR, ECG, Echo), GI (celiac screen, inflammatory markers, malabsorption), renal (urinalysis), liver (enzymes, albumin)

**Table 9. Failure to Thrive Patterns**

| Growth Parameters | | | Suggestive Abnormality | |
|---|---|---|---|---|
| Decreased Wt | Normal Ht | Normal HC | Caloric insufficiency<br>Decreased intake | Hypermetabolic state<br>Increased losses |
| Decreased Wt | Decreased Ht | Normal HC | Structural dystrophies<br>Endocrine disorder | Constitutional growth delay (BA < CA)<br>Familial short stature (BA = CA) |
| Decreased Wt | Decreased Ht | Decreased HC | Intrauterine insult | Genetic abnormality |

BA = bone age; CA = chronological age; HC = head circumference; Ht = height; Wt = weight





**Mid-Parental Height**
- Boys target height = (father ht + mother ht + 13) / 2
- Girls target height = (father ht + mother ht – 13) / 2

**Note:** height should be taken in cm



**Clinical Signs of FTT**

**SMALL KID**
**S**ubcutaneous fat loss
**M**uscle atrophy
**A**lopecia
**L**ethargy
**L**agging behind normal
**K**washiorkor
**I**nfection (recurrent)
**D**ermatitis



**Upper to Lower Segment Ratio**
- **Increased** in achondroplasia, short limb syndromes, hypothyroid, storage diseases
- **Decreased** in Marfan's, Klinefelter's, Kallman's syndromes, and testosterone deficiency
- **Calculation:** upper segment/lower segment
  - Upper segment: top of head to pubic symphysis
  - Lower segment: pubic symphysis to floor

### Etiology
- an interplay between pathophysiology and psychosocial influences
- investigations should assess:
  1. complex factors in the parent-child relationship
     - dietary intake, knowledge about feeding, improper mixing of formula
     - feeding environment
     - parent-child interaction, attachment
     - child behaviours, hunger/satiety cues
     - postpartum depression
     - social factors: stress, poverty, neglect, child/domestic abuse, parental substance abuse, restricted diets
  2. inadequate caloric intake: inadequate milk supply/latching, mechanical feeding difficulty (cleft palate), oromotor dysfunction, toxin-induced anorexia
  3. inadequate absorption: biliary atresia, celiac, IBD, CF, inborn errors of metabolism, milk protein allergy, pancreatic cholestatic conditions
  4. increased metabolism: chronic infection, CF, lung disease from prematurity, hyperthyroidism, asthma, IBD, malignancy, renal failure

### Management
- most as outpatient using multidisciplinary approach: primary care physician, occupational therapist, dietitian, psychologist, social work, CAS
- medical: oromotor problems, iron-deficiency anemia, gastro-esophageal reflux
- nutritional: educate about age-appropriate foods, calorie boosting, mealtime schedules, and environment; goal to reach 90-110% IBW, correct nutritional deficiencies, and promote catch-up growth/development
- behavioural: positive reinforcement, mealtime environment, no distractions (e.g. toys, books, or TV) during mealtime

### Energy Requirements
- see *Nutrition*, P6

## Obesity

- **definition**: overweight is BMI >85th percentile; obesity is BMI >95th percentile for age and height
- **risk factors**: genetic predisposition (e.g. both parents obese – 80% chance of obese child), psychosocial/environmental contributors
- **etiology**: organic causes are rare (<5%), but may include Prader-Willi, Carpenter, Turner, Cushing syndromes, hypothyroidism
- **complications**: association with HTN, dyslipidemia, slipped capital femoral epiphysis, type 2 DM, asthma, obstructive sleep apnea, gynecomastia, polycystic ovarian disease, early menarche, irregular menses, psychological trauma (e.g. bullying, decreased self-esteem, unhealthy coping mechanisms, depression)
- childhood obesity often persists into adulthood
- **investigations**: BP, pulse, screen for: dyslipidemia, fatty liver disease (ALT), type 2 DM (based on risk factors)
- **management**
  - encouragement and reassurance; engagement of entire family
  - diet: qualitative changes (do not encourage weight loss, but allow for linear growth to catch up with weight), special diets used by adults and very low calorie diets are not encouraged
  - behaviour modification: increase activity, change eating habits/meal patterns, limit juice/sugary drinks, ensure adequate sleep
  - education: multidisciplinary approach, dietitian, counselling
  - surgery and pharmacotherapy are rarely used in children
  - increase physical activity (1 h/d), reduce screen time (<2 h/d)
  - small changes in energy expenditure and intake (lose 1 lb/mo)
  - long term goal: maintain BMI <85th percentile

## Poison Prevention

- keep all types of medicines, vitamins, and chemicals locked up in a secure container
- potentially dangerous: medications, illicit drugs, drain cleaners, furniture polish, insecticides, cosmetics, nail polish remover, automotive products
- do not store any chemicals in juice, soft drink, or water bottles
- keep alcoholic beverages out of reach: 3 oz hard liquor can kill a 2 yr old
- always read labels before administering medicine to ensure correct medication drug and dose and/or speak with a pharmacist or healthcare provider



**Perinatal and Early Childhood Factors for Overweight and Obesity in Young Canadian Children**
Can J Public Health 2013;104(1):e69-74
**Purpose**: To assess potential early-life factors and their interrelationships with obesity among young Canadian children.
**Methods**: Data from a nationally representative sample of children aged 6-11 yr in the Canadian Health Measures Survey were analyzed. The associations of perinatal and early childhood behaviours and socioeconomic factors with overweight or obesity were evaluated using multivariate logistic regression models.
**Results**: Of 968 term-born children, 21% were overweight and another 13% were obese. Maternal smoking during pregnancy was positively associated with obesity. This association was mediated by birth weight and once controlled, the strength of the association between smoking and child obesity increased by 12%. Birth weight per 100 g (1.05; 1.005-1.09) was significantly associated with obesity. Exclusive breastfeeding for 6 mo, adequate sleep hours, and being physically active were found to be protective. Breastfeeding, whether exclusive or not, significantly reduced obesity risk among children whose mothers never smoked in pregnancy.
**Conclusion**: This study identified multiple perinatal and childhood factors associated with obesity in young Canadian children. Effective prevention strategies targeting four modifiable maternal and child risk factors may reduce childhood obesity by up to 54% in Canada.



**Screen Time Guidelines (Canadian Society for Exercise Physiology)**
- Screen time is not recommended for children under 2 yr
- <1 h/d screen time is appropriate for children aged 2-5 yr
- <2 h/d screen time is appropriate for children 5-17 yr

# Rashes

**Table 10. Common Pediatric Rashes**

| Type of Rash | Differential | Appearance | Management |
|---|---|---|---|
| **Diaper Dermatitis** | Irritant contact dermatitis | Shiny, red macules/patches, no skin fold involvement | Eliminate direct skin contact with urine and feces, allow periods of rest without a diaper, frequent diaper changes, topical barriers (petrolatum, zinc oxide or paste), short-term low-potency topical corticosteroids (severe cases) |
| | Seborrheic dermatitis | Yellow, greasy macules/ plaques on erythema, scales | Short-term, moisturisers, topical antifungal (ketoconazole), low-potency topical corticosteroids |
| | Candidal dermatits | Erythematous macerated papules/plaques, satellite lesions, involvement of skin folds | Antifungal agents (e.g. clotrimazole, nystatin) |
| **Other Dermatitis** | Atopic dermatitis | Erythematous, papules/ plaques, oozing, excoriation, lichenification, classic areas of involvement | Eliminate exacerbating factors, maintain skin hydration (daily baths and moisturisers), corticosteroids,, topical calcineurin inhibitor (2nd line) |
| | Nummular dermatitis | Annular erythematous plaques, oozing, crusting | Avoid irritant if identified, potent topical steroid in emollient base, short-term systemic steroids ± antibiotics (severe) |
| | Allergic contact dermatitis | Red papules/plaques/vesicles/ bullae, only in area of allergen | Mild: soothing lotion (e.g. calamine lotion)<br>Moderate: low-to-intermediate potency topical corticosteroids<br>Severe: systemic corticosteroids and antihistamine |
| | Irritant contact dermatitis | Morphology depends on irritant | Avoid skin contact |
| | Dyshidrotic dermatitis | Papulovesicular, cracking/ fissuring, hands and feet ("tapioca pudding") | Mild/moderate: medium/potent topical corticosteroids<br>Severe: systemic corticosteroids, local PUVA or UVA treatments |
| **Infectious** | Scabies | Polymorphic (red excoriated papules/nodules, burrows), in web spaces/folds, very pruritic Often affects multiple family members | Permethrin (Nix®) 5% cream for patient and family (2 applications, 1 wk apart) |
| | Impetigo | Honey-coloured crusts or superficial bullae | Topical antibiotics if mild: fucidic acid or mupirocin cream; Oral antibiotics if severe (e.g. cephalexin/erythromycin) |
| | Tinea corporis | Round erythematous plaques, central clearing and scaly border | Topical anti-fungal for skin, systemic anti-fungals for nails/head |
| Pediatric Exanthems (see *Infectious Pediatric Exanthems*, P53) | | | |
| Acne (see Dermatology, D11) | | | |

# Sleep Disturbances

## Types of Sleep Disturbances

- insufficient sleep quantity
  - difficulty falling asleep (e.g. limit setting sleep disorder)
    - preschool and older children
    - bedtime resistance
    - due to caregiver's inability to set consistent bedtime rules and routines
    - often exacerbated by child's oppositional behaviours
- poor sleep quality
  - frequent arousals (e.g. sleep-onset association disorder)
    - infants and toddlers
    - child learns to fall asleep only under certain conditions or associations (e.g. with parent, held, rocked or fed, with light on, in front of television), and loses ability to self-soothe
    - during the normal brief arousal periods of sleep (q90-120 min), child cannot fall back asleep because same conditions are not present
- obstructive sleep apnea
  - **definition**: partial or intermittent complete airway obstruction during sleep causing disrupted ventilation and sleep pattern
  - **epidemiology**: 1-5% of preschool aged children, more common in African American children
  - **clinical features**: snoring/gasping/noisy breathing during sleep and irritable/tired/hyperactive during the day
  - **complications**: cardiovascular (HTN/LV remodelling due to sympathetic activation), growth, cognitive, and behavioural deficitis
  - **etiology**: adenotonsillar hypertrophy, craniofacial abnormalities, obesity



**Daily Sleep Requirement**
- <6 mo 16 h
- 6 mo 14.5 h
- 12 mo 13.5 h
- 2 yr 13 h
- 4 yr 11.5 h
- 6 yr 9.5 h
- 12 yr 8.5 h
- 18 yr 8 h

**Nap Patterns**
- 2/d at 1 yr
- 1/d at 2 yr: 2-3 h
- 0.5/d at 5 yr: 1.7 h

  - **investigations**: polysomnography is gold standard for diagnosis but not required (expensive, inaccessible)
  - **management**: adenotonsillectomy and weight management are first-line tx, follow-up for residual OSA. Watchful waiting acceptable in mild-moderate cases
    - adenotonseillectomy does not improve executive function/attention but improves behaviour, QOL, polysymnographic findings
    - use CPAP if adenotonsillectomy is contraindicated (cleft palate/bleeding disorder/acute tonsillitis), OSA w/ minimal adenotonsillar tissue, residual OSA
    - avoid pollutants/tobacco smoke, allergens
    - avoid use of corticosteroids and antibiotics
- parasomnias
  - episodic nocturnal behaviours (e.g. sleepwalking, sleep terrors, nightmares)
  - often involves cognitive disorientation and autonomic/skeletal muscle disturbance

### Management of Sleep Disturbances
- set strict bedtimes and "wind-down" routines
- do not send child to bed hungry
- positive reinforcement for: limit setting sleep disorder
- always sleep in own bed, in a dark, quiet, and comfortable room
- avoid screens before bedtime and avoid caffeine-containing food
- do not use bedroom for timeouts
- systematic ignoring and gradual extinction for: sleep-onset association disorder

### Nightmares
- **epidemiology**: common in boys, 4-7 yr old
- associated with REM sleep (anytime during night)
- **clinical feature**: upon awakening, child is alert and clearly recalls frightening dream ± associated with daytime stress/anxiety
- **management**: reassurance

### Night Terrors
- **epidemiology**: 15% of children have occasional episodes
- usually in first one third of night; arousal from deep (slow wave) sleep
- **clinical feature**: abrupt sitting up, eyes open, screaming/vocalization, occurs in early hours of sleep, stage 4 of sleep; signs of autonomic arousal with no memory of event, disoriented if awakened, inconsolable, stress/anxiety can aggravate them
- **management**: reassurance from parents, ensure child is safe (e.g. if sleepwalks), often remits spontaneously at puberty

## Sudden Infant Death Syndrome

### Definition
- sudden and unexpected death of an infant <12 mo of age in which the cause of death cannot be found by history, examination, or a thorough postmortem and death scene investigation

### Epidemiology
- 0.5/1000 (leading cause of death between 1-12 mo of age); M:F = 3:2
- more common in children placed in prone position
- in full term infants, peak incidence is 2-4 mo, 95% of cases occur by 6 mo
- increase in deaths during peak RSV season
- most deaths occur between midnight and 8 AM

### Risk Factors
- prematurity (<37 wk), early bed sharing (<12 wk), alcohol use during pregnancy, soft bedding, low birthweight, Indigenous background, male, no prenatal care, smoking in household, prone sleep position, poverty
- risk of SIDS is increased 3-5x in siblings of infants who have died of SIDS
- bed sharing: sleeping on a sofa, adult sleeping with an infant after consumption of alcohol/street drugs or extreme fatigue, sleeping on a surface with a fixed wall (couch/sofa), infant sleeping with someone other than primary caregiver

### Prevention
- "Back to Sleep, Front to Play" (place infant on back when sleeping, daily supervised play/"tummy time" in prone position)
- avoid sharing bed with infant
- avoid overheating and overdressing
- appropriate infant bedding (firm mattress, avoid loose bedding, pillows, stuffed animals, and crib bumper pads)
- exclusive breastfeeding in first mo and no smoking
- pacifiers appear to have a protective effect; do not reinsert if falls out during sleep
- infant monitors do not reduce incidence

**Brief Resolved Unexplained Events (BRUE)**
These are sudden, brief and now resolved episodes in an infant with one or more of the following: cyanosis or pallor; absent, decreased or irregular breathing; change in tone; and/or altered level of consciousness. The observer fears the child may be dying. The child should be asyptomatic on presentation and there is no explanation after a history and physical for the cause. There is no clear connection between most BRUEs and SIDS. Evaluating for a cause of the BRUE (e.g. infection, cardiac, neurologic) is guided by history, physical exam, and period of observation

# Adolescent Medicine

## Adolescent History (HEEADSSS)

- tailor your history according to the clinical context

**Home:** Who do you live with? What kind of place do you live in? Do you get along with your parents and/or siblings?

**Education/Employment:** What grade are you in? What are your favourite subjects? What was your average on your last report card (ask for changes)? How much school have you missed this past year? Do you work (if so, how much)? Do you get along with teachers/employers?

**Eating:** Tell me about your meals/snacks in a typical day. Have you ever gone on a diet? What are your favourite and least favourite foods? (see Psychiatry, *Eating Disorders*, PS34)

**Activities:** What do you do after school? On the weekends? How much time do you spend on the computer/watching TV every day? Do you use social media (i.e. Facebook, Twitter, Instagram, etc.)? What do you do with your friends outside of school?

**Drugs:** Which seems to be more popular at your school, alcohol or drugs? How often do you drink/smoke marijuana or cigarettes/take other drugs? Have you ever passed out or not been able to remember what happened? Has anything bad ever happened to you while you were drunk or stoned?

- can organize as a CRAFFT screen:
  - Part A: during the last 12 mo, did you:
    1. Drink any alcohol?
    2. Smoke any marijuana or hashish?
    3. Use anything else to get high?
  - Part B:
    1. Have you ever ridden in a car driven by someone (including yourself) who was high or had been using drugs/alcohol?
    2. Do you ever use drugs/alcohol to relax, feel better about yourself, or fit in?
    3. Do you ever use drugs/alcohol when you are alone?
    4. Do you ever forget things you did while using drugs/alcohol?
    5. Do your family/friends ever tell you that you should cut down on your drinking or drug use?
    6. Have you ever gotten into trouble while you were using drugs/alcohol?
- see Psychiatry, *Substance Abuse*, PS25

**Sexuality:** Are you romantically interested in anyone? When you think about having sex with someone, do you think about females, males, or both? Have you ever had sex with anyone? Whether the answer is yes or no, the next question is: What activities would you include in the term 'having sex'? What do you do to prevent getting a STI/getting pregnant/getting someone pregnant? Has anyone ever given you money, drugs, or other stuff in exchange for sex? (see Gynecology, *Sexually Transmitted Infections*, GY26)

**Suicidality/Depression:** On a scale of 1 to 10, where 1 is so sad that you might kill yourself and 10 is the happiest you could be, where are you most days? Have you lost interest in activities that you used to enjoy? Do you often have trouble sleeping (Is there a difference between school days and the weekend?)? Have you ever thought seriously about suicide? Did you make a plan? (see Psychiatry, *Depression/Suicide*, PS12, PS5)

**Safety/Violence:** Do you ever get into a car with a driver who has been drinking? Do you always wear a seatbelt/bicycle helmet? Are you being bullied at school? Has anyone ever touched you in an unwanted way?

See *Disorders of Sexual Development*, P30

**Adolescent Psychosocial Assessment**

**HEEADSSS**
**H**ome
**E**ducation/Employment
**E**ating
**A**ctivities
**D**rugs
**S**exuality
**S**uicide and depression
**S**afety/violence

Rates of drug use in high school students who have used in the past year: alcohol (58.2%), cannabis (25.6%), tobacco (11.7%)

**Consent and Close Age Exceptions**

- The age of consent is 16
- A youth 16 or 17 cannot consent if: the partner is in a position of trust/authority (e.g. coach, teacher), young person is dependent on the partner (e.g. for care or support), the relationship is exploitative (e.g. prostitution or pornography)
- A 14 or 15-year old can consent as long as the partner is less than 5 years older and as long as there is no relationship of trust, authority, dependency, or exploitation
- A 12 or 13-year old can consent as long as the partner is less than 2 years older and as long as there is no relationship of trust, authority, dependency, or exploitation

Date rape comprises 80% of sexual assault in teenagers

Prevalence of depression: 1-2% in pre-pubertal children and 6-8% in adolescents

**Table 11. Developmental Stages of Adolescence**

| | Early Adolescence (10-13 yr) | Middle Adolescence (14-16 yr) | Late Adolescence (17-19 yr) |
|---|---|---|---|
| **Cognitive and moral** | Concrete<br>Unable to perceive long-term outcome of current decision-making | Emergence of abstract thought<br>Questioning mores | Future oriented with sense of perspective<br>Idealism<br>Ability to think things through independently |
| **Self-concept/identity formation** | Preoccupied with changing body<br>Self-consciousness about appearance and attractiveness | Concern with attractiveness<br>"Stereotypical adolescent" | More stable body image<br>Attractiveness may still be of concern<br>Firmer identity |
| **Family** | Increased need for privacy | Conflicts over control and independence<br>Struggle for acceptance of greater autonomy | Emotional and physical separation from family<br>Increased autonomy |
| **Peers** | Seeks same-sex peer affiliation to counter instability | Intense peer group involvement<br>Preoccupation with peer | Peer group and values recede in importance<br>Intimacy/possible commitment takes precedence |
| **Sexual** | Increased interest in sexual anatomy<br>Anxieties and questions about genital changes, size<br>Limited dating and intimacy | Testing ability to attract partner<br>Initiation of relationships and sexual activity<br>Questions of sexual orientation | Consolidation of sexual identity<br>Focus on intimacy and formation of stable relationships |

# Child Abuse and Neglect

### Definition
- an act of commission (physical, sexual, or psychological abuse) or omission (neglect) by a caregiver that harms a child

### Legal Duty to Report
- upon reasonable grounds to suspect abuse and/or neglect, physicians are required by legislation to contact the CAS to personally disclose all information relevant to the child's safety concern
- duty to report overrides patient confidentiality; physician is protected against liability

### Ongoing Duty to Report
- if there are additional reasonable grounds to suspect abuse and/or neglect, a further report to the CAS must be made

### Risk Factors
- environmental factors: social isolation, poverty, domestic violence
- caregiver factors: personal history of abuse, psychiatric illness, postpartum depression, substance abuse, single parent family, poor social and vocational skills, below average intelligence
- child factors: difficult temperament, disability, special needs (e.g. developmental delay), premature

### Management of Physical Abuse, Child Abuse, and Neglect
- do not take an abuse history from a young child; this must be done by trained personnel (e.g. during a forensic interview)
- report all suspicions to CAS; request emergency visit if imminent risk to child or any siblings in the home
- acute medical care: hospitalize for medical evaluation or treatment of injuries if indicated
- arrange consultation from social work and appropriate follow-up

# Physical Abuse

### History
- history that is not compatible with physical findings or with child's developmental capabilities
- history not reproducible or changes dramatically over time
- delay in seeking medical attention that is unexplained by other factors
- assess previous trauma or hospitalizations
- ask FHx: bleeding disorder, bone disorder, metabolic conditions
- ask developmental history

### Physical Exam
- physical findings not explained by underlying medical condition
- growth parameters including past recorded parameters (weight, height, head circumference)
- multiple injuries not explained by accidental injury or child's development level
- patterned skin injuries: linear, shapes, etc. that do not match provided history
- injury location:
  - bruises: on areas with abundant soft-tissue cushioning, such as abdomen, buttocks, genitalia, fleshy part of cheek or on ears, neck or feet, bruises that do not fit described cause
  - fractures: posterior rib/metaphyseal/scapular/vertebral/sternal fractures (more suspicious for non-accidental injuries)
  - immersion burns (e.g. hot water)
- altered mental status: head injury, poisoning
- eyes – retinal hemorrhages
- scalp – patchy hair loss from traumatic alopecia or severe malnutrition
- oral exam – check the frenula for tears
- head trauma is the leading cause of death in child maltreatment (e.g. acceleration-deceleration forces [shaking], direct force application [blow or impact])
- consider "red herrings" (e.g. slate grey macule/congenital dermal melanocytosis vs. bruises)

**Medical Assessment of Bruising in Suspected Child Maltreatment Cases**
Paediatr Child Health 2013;18(8):433-7
**CPS Position Statement**: While bruises are most often due to minor accidental injury, they may also signal underlying medical illness or inflicted injury. Knowing when to assess bruises in the context of maltreatment can be challenging. The following are red flags for inflicted injury in such bruising cases:
- Babies not yet cruising
- Present on ears, neck, feet, buttocks or torso
- Not on the front of the body and/or overlying bone
- Unusually large or numerous
- Clustered or patterned
- Not fitting with the described causal mechanism

### Investigations
- document all injuries on a body diagram: type, location, size, shape, colour, pattern
  - photography of skin injuries is ideal (police or hospital photography preferred; do not use physician's personal camera)
- rule out medical causes of bruising/fracture with appropriate investigations (e.g. blood disorders or rickets):
  - if fractures evident: $Ca^{2+}$, $Mg^{2+}$, $PO_4^{3-}$, ALP, PTH, Vitamin D, albumin
  - if bruising present: CBC, INR, PTT, von Willebrand factor, factors VIII/IX
- screen for abdominal trauma
  - transaminases and amylase if elevated: abdo CT recommended
  - renal function – electrolytes, urinalysis
    - toxicology screen – overdose or poisoning
- skeletal survey in children <2 yr; select imaging based on history in children >5 yr
  - neuroimaging: CT and/or MRI - dilated eye examination by pediatric ophthalmologist to rule out retinal hemorrhage if subdural hemorrhage detected on head imaging

# Sexual Abuse

### Epidemiology
- peak ages at 2-6 yr and 12-16 yr, most do not report until adulthood
- as adults: more likely to develop obesity, sexual problems, IBS, fibromyalgia, STI, substance use disorder
- more likely to experience intimate partner violence and sexual assault
  - in decreasing order: family member, non-relative known to victim, stranger

### History
- psychosocial: specific or generalized fears, depression, nightmares, social withdrawal, lack of trust, low self-esteem, school failure, sexually aggressive behaviour, advanced sexual knowledge, sexual preoccupation or play

### Physical Exam
- recurrent UTIs, pregnancy, STIs, vaginitis, vaginal bleeding, pain, genital injury, enuresis
  - anogenital exam performed along with head-to-toe physical for physical trauma
  - instrumentation not required for anogenital exam, speculum contraindicated in prepubertal girls
  - most victims have normal anogenital exam – cannot rule out sexual abuse if exam is negative

### Investigations
- depend on presentation, age, sex, and pubertal development of child
  - sexual assault examination kit within 24 h if prepubertal, within 72 h if pubertal
  - rule out STI, UTI, pregnancy (consider STI prophylaxis or emergency contraception)
  - rule out other injuries (vaginal/anal/oral penetration, fractures, head trauma)
  - investigations to rule out drug and alcohol screen e.g. Rohypnol, 'Liquid G,' etc.

# Neglect

### Definition
- omissions in care by parents or caregiver that leads to actual or potential harm

### History
- from child and each caregiver separately (if possible)

### Physical Exam
- head to toe (do not force), growth parameters, nutrition status
- dental care
- emotional state

### Investigations
- blood tests to rule out medical conditions or nutritional deficiencies (e.g. thrombocytopenia or coagulopathy)



**Presentation of Neglect**
- FTT, developmental delay
- Inadequate or dirty clothing, poor hygiene
- Child exhibits poor attachment to parents, no stranger anxiety

# Cardiology

## Congenital Heart Disease

### PRENATAL CIRCULATION

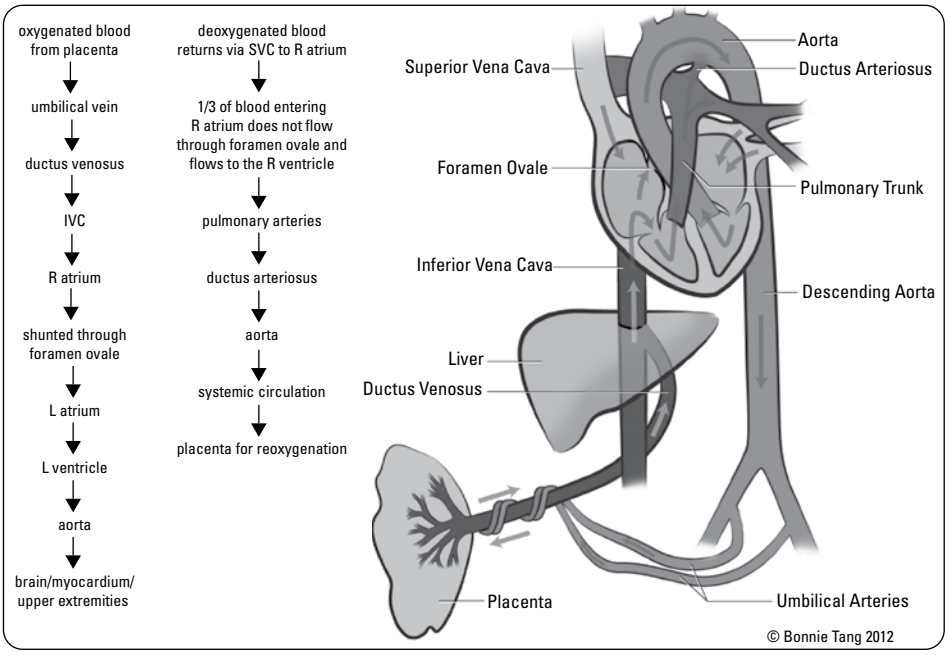



**Figure 1. Prenatal circulation**

Fetal circulation is designed so that oxygenated blood is preferentially delivered to the brain and myocardium

#### Before Birth

- shunting deoxygenated blood
  - ductus arteriosus: connection between pulmonary artery and aorta
- shunting oxygenated blood
  - foramen ovale: connection between right and left atria
  - ductus venosus: connection between umbilical vein and inferior vena cava

#### At Birth

- with first breath, lungs open up → pulmonary resistance decreases → pulmonic blood flow increases
- separation of low resistance placenta → systemic circulation becomes a high resistance system → ductus venosus closure
- increased pulmonic flow → increased left atrial pressures → foramen ovale closure
- increased oxygen concentration in blood after first breath → decreased prostaglandins → ductus arteriosus closure
- closure of fetal shunts and changes in vascular resistance → infant circulation assumes normal adult flow

#### Epidemiology

- 8/1000 live births have CHD, which may present as a heart murmur, heart failure, or cyanosis; VSD is the most common lesion

#### Investigations

- Echo, ECG, CXR
- pre and postductal oxygen saturations, 4 limb BPs, hyperoxia test

### CYANOTIC VS. ACYANOTIC CONGENITAL HEART DISEASE

- cyanosis: blue mucous membranes, nail beds, and skin secondary to an absolute concentration of deoxygenated hemoglobin of at least 30 g/dL
- acyanotic heart disease (i.e. L to R shunt, obstruction occurring beyond lungs): blood passes through pulmonic circulation → oxygenation takes place → low levels of deoxygenated blood in systemic circulation → no cyanosis
- cyanotic heart disease (i.e. R to L shunt): blood bypasses the lungs → no oxygenation occurs → high levels of deoxygenated hemoglobin enters the systemic circulation → cyanosis

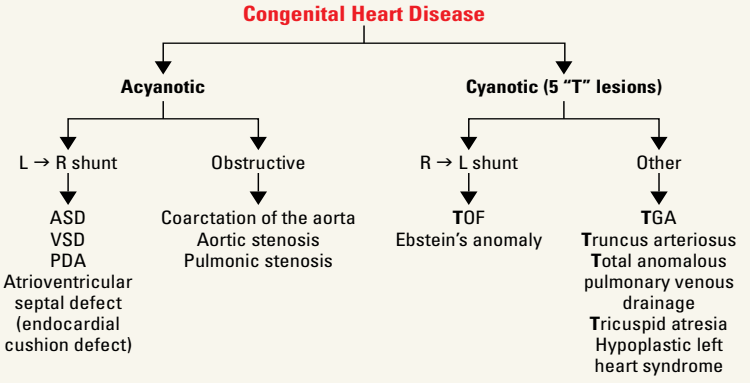



**Figure 2. Common congenital heart diseases**

**Characteristic CXR Findings in CHD**
- Boot-shaped heart: tetralogy of Fallot, tricuspid atresia
- Egg-shaped heart: transposition of great arteries
- "Snowman" heart: total anomalous pulmonary venous return

# Acyanotic Congenital Heart Disease

## 1. LEFT-TO-RIGHT SHUNT LESIONS

- extra blood is displaced through a communication from the left to the right side of the heart → increased pulmonary blood flow → increased pulmonary pressures
- shunt volume is dependent upon three factors: (1) size of defect, (2) pressure gradient between chambers or vessels, and (3) peripheral outflow resistance
- untreated shunts can result in pulmonary vascular disease, left ventricular dilatation and dysfunction, right ventricular HTN and RVH, and ultimately R to L shunts

### Atrial Septal Defect

- 3 types: *ostium primum* (common in DS, defect located at mitral or tricuspid valves), *ostium secundum* (most common type, 50-70%, defect located at septum between left and right atria), *sinus venosus* (defect located at entry of superior vena cava into right atrium)
- **epidemiology**: 6-8% of congenital heart lesions, common in patients with certain congenital disorders (e.g. Down's syndrome, fetal alcohol syndrome)
- **natural history**
  - 80-100% spontaneous closure rate if ASD diameter <8 mm
  - if remains patent, CHF and pulmonary HTN can develop in adult life
- **clinical feature**
  - history: often asymptomatic in childhood
  - physical exam: grade 2-3/6 pulmonic outflow murmur, widely split, and fixed S2
  - children with large ASDs may have signs of heart failure (tachypnea, FTT, hepatomegaly, pulmonary rales/retractions)
- **investigations**
  - ECG: RAD, mild RVH, RBBB (normal ECG does not rule out)
  - CXR: increased pulmonary vasculature, cardiac enlargement (normal ECG does not rule out)
  - Echo: diagnostic
- **management**
  - elective surgical or catheter closure between 2-5 yr of age, though majority require no surgery
  - size <8 mm will likely spontaneously close

### Ventricular Septal Defect

- most common congenital heart defect (30-50%)
- small VSD (majority)
  - **clinical feature**
    - history: asymptomatic, normal growth, and development
    - physical exam: early systolic to holosystolic murmur, best heard at LLSB, thrill
  - **investigations**: Echo to confirm diagnosis (ECG and CXR are normal)
  - **management**: most close spontaneously
- moderate-to-large VSD
  - **epidemiology**: CHF by 2 mo; late secondary pulmonary HTN if left untreated
  - **clinical feature**
    - history: delayed growth, decreased exercise tolerance, recurrent URTIs or "asthma" episodes
    - physical exam: holosystolic murmur at LLSB, mid-diastolic rumble at apex, size of VSD is inversely related to intensity of murmur, loss of splitting of second heart sound and a loud P2 suggests pulmonary hypertension
  - **investigations**
    - ECG: LVH, LAH, RVH (normal ECG does not rule out)
    - CXR: increased pulmonary vasculature, cardiomegaly, CHF (normal CXR does not rule out)
    - Echo: diagnostic
  - **management**: treatment of CHF and surgical closure by 1 yr old, if surgery required

Moderate-to-Large VSD
Size of VSD is inversely related to intensity of murmur

### Patent Ductus Arteriosus

- patent vessel between descending aorta and left pulmonary artery (normally, functional closure within first 15 h of life, anatomical closure within first days of life)
- **epidemiology**
  - 5-10% of all congenital heart defects
  - delayed closure of ductus is common in premature infants (1/3 of infants <1750 g); this is different from PDA in term infants
- **natural history**: spontaneous closure common in premature infants, less common in term infants
- **clinical feature**
  - history: asymptomatic, or have apneic or bradycardic spells, poor feeding, accessory muscle use, CHF
  - physical exam: tachycardia, bounding pulses, hyperactive precordium, wide pulse pressure, continuous "machinery" murmur best heard at left infraclavicular area
- **investigations**
  - ECG: may show left atrial enlargement, LVH, RVH
  - ECHO is diagnostic
  - CXR: may show normal to mildly enlarged heart, increased pulmonary vasculature, prominent pulmonary artery
- **management**
  - indomethacin (Indocid®): antagonizes prostaglandin E2, which maintains ductus arteriosus patency; only effective in premature infants
  - catheter or surgical closure if PDA causes respiratory compromise, FTT, or persists beyond 3rd mo of life

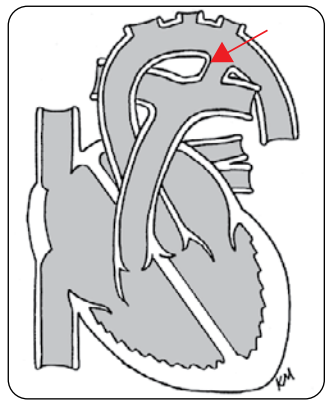


Figure 3. Patent duct arteriosus

**Physical Exam for PDA (in term infant)**
- Heavy "machinery" murmur
- High pulse rate
- Wide pulse pressure
- Hyperactive precordium
- Big bounding pulse

## 2. OBSTRUCTIVE LESIONS

- present with decreased urine output, pallor, cool extremities and poor pulses, shock, or sudden collapse

### Coarctation of the Aorta

- **definition**: narrowing of aorta (almost always at the level of the ductus arteriosus)
- **epidemiology**: commonly associated with bicuspid aortic valve (50%); Turner syndrome (35%)
- **clinical feature**
  - history: often asymptomatic
  - physical exam
    - blood pressure discrepancy between upper and lower extremities (increased suspicion/severity if >20 mmHg difference)
    - diminished or delayed femoral pulses relative to brachial (i.e. brachial-femoral delay)
    - possible systolic murmur with late peak at apex, left axilla, and left back
    - if severe, presents with shock in the neonatal period when the ductus arteriosis closes
- **investigations**: ECG shows RVH early in infancy, LVH later in childhood; Echo or MRI for diagnosis
- **prognosis**: can be complicated by HTN; if associated with other lesions (e.g. PDA, VSD) can lead to CHF
- **management**: give prostaglandins to keep ductus arteriosus patent for stabilization and perform surgical correction in neonates; for older infants and children balloon arterioplasty may be an alternative to surgical correction

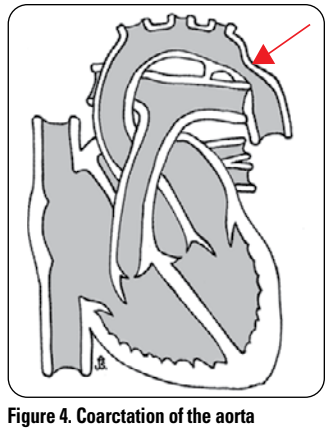


Figure 4. Coarctation of the aorta

### Aortic Stenosis

- 4 types: valvular (75%), subvalvular (20%), supravalvular, and idiopathic hypertrophic subaortic stenosis (5%)
- **clinical feature**
  - history: often asymptomatic, but may be associated with CHF, exertional chest pain, syncope, or sudden death
  - physical exam: SEM at RUSB with aortic ejection click at the apex (only for valvular stenosis)
- **investigations**: echo for diagnosis
- **management**: valvular stenosis is usually treated with balloon valvuloplasty, patients with subvalvular or supravalvular stenosis require surgical repair, exercise restriction required

### Pulmonary Stenosis

- 3 types: valvular (90%), subvalvular, or supravalvular
- **definition of critical pulmonary stenosis**: inadequate pulmonary blood flow, dependent on ductus for oxygenation, progressive hypoxia and cyanosis
- **natural history**: may be part of other congenital heart lesions (e.g. Tetralogy of Fallot) or in association with syndromes (e.g. congenital rubella, Noonan syndrome)
- **clinical feature**
  - history: spectrum from asymptomatic to CHF
  - physical exam: wide split S2 on expiration, SEM at LUSB, pulmonary ejection click (for valvular lesions)
- **investigations**
  - ECG findings: RVH
  - CXR: post-stenotic dilation of the main pulmonary artery (due to high velocity jet past stenotic valve)
  - Echo: diagnostic
- **management**: surgical repair if critically ill or if symptomatic in older infants/children

# Cyanotic Congenital Heart Disease

- systemic venous return re-enters systemic circulation directly
- most prominent feature is cyanosis ($O_2$ sat <75%)
- hyperoxic test differentiates between cardiac and other causes of cyanosis
  - obtain preductal, right radial ABG in room air, then repeat after the child inspires 100% $O_2$
  - if $PaO_2$ improves to > mmHg, cyanosis less likely cardiac in origin
- pre-ductal and post-ductal pulse oximetry
  - >5% difference suggests R to L shunt

**Causes of Cyanotic Heart Disease – 5T's**
**T**runcus arteriosus
**T**ransposition of the great vessels
**T**ricuspid atresia
**T**etralogy of Fallot
**T**otal anomalous pulmonary venous return

## 1. RIGHT-TO-LEFT SHUNT LESIONS

### Tetralogy of Fallot

- **epidemiology**: 10% of all CHD, most common cyanotic heart defect diagnosed beyond infancy with peak incidence at 2-4 mo of age
- **pathophysiology**
  - embryological defect due to anterior and superior deviation of the outlet septum leading to: VSD, RVOTO (i.e. pulmonary stenosis ± subpulmonary valve stenosis), over-riding aorta, and RVH
    - infants may initially have a L → R shunt (therefore no cyanosis); however, RVOTO is progressive, leading to increasing R → L shunting with hypoxemia and cyanosis
    - degree of RVOTO determines the direction and degree of shunt and, therefore, the extent of clinical cyanosis and degree of RVH
- **clinical feature**
  - history: hypoxic "tet" spells
    - during exertional states (crying, exercise) the increasing pulmonary vascular resistance and decrease in systemic resistance causes an increase in right-to-left shunting
    - clinical features include paroxysms of rapid and deep breathing, irritability and crying, increasing cyanosis, decreased intensity of murmur (decreased flow across RVOTO), patient squatting for relief (increased peripheral resistance, decreased R to L shunting)
    - if severe, can lead to decreased level of consciousness, seizures, death
  - physical exam
    - single loud S2 due to severe pulmonary stenosis (i.e. RVOTO), SEM at LSB
- **investigations**
  - ECG: RAD, RVH
  - CXR: boot-shaped heart, decreased pulmonary vasculature, right aortic arch (in 20%)
  - Echo: diagnostic
- **management of spells**: $O_2$, knee-chest position, fluid bolus, morphine sulfate, propranolol
- **treatment**: surgical repair at 4-6 mo of age; earlier if marked cyanosis or "tet" spells

**Tetralogy of Fallot**
1. VSD
2. RVOTO
3. Aortic root "overriding" VSD
4. RVH

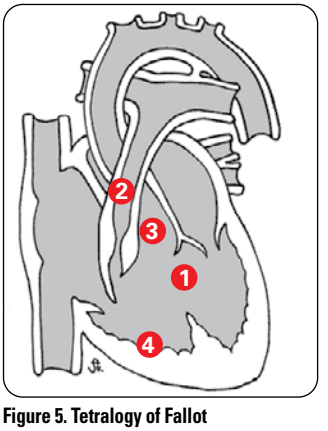



**Figure 5. Tetralogy of Fallot**

## 2. OTHER CYANOTIC CONGENITAL HEART DISEASES

### Transposition of the Great Arteries (TGA)

- **epidemiology**: 3-5% of all congenital cardiac lesions, most common cyanotic CHD in neonates
- **pathophysiology**: parallel pulmonary and systemic circulations
  - systemic: body → RA → RV → aorta → body
  - pulmonary: lungs → LA → LV → pulmonary artery → lungs
  - survival is dependent on mixing through PDA, ASD, or VSD
- **physical exam**
  - neonates: ductus arteriosus closure causes rapidly progressive severe hypoxemia unresponsive to oxygen therapy, acidosis, and death
  - VSD present: cyanosis is not prominent; CHF within first weeks of life
  - VSD absent: no murmur
- **investigations**
  - ECG: RAD, RVH, or may be normal
  - CXR: egg-shaped heart with narrow mediastinum ("egg on a string")
  - Echo: diagnostic
- **management**
  - symptomatic neonates: prostaglandin E1 infusion to keep ductus open until balloon atrial septostomy
  - surgical repair: arterial switch performed in the first two weeks in those without a VSD while LV muscle is still strong

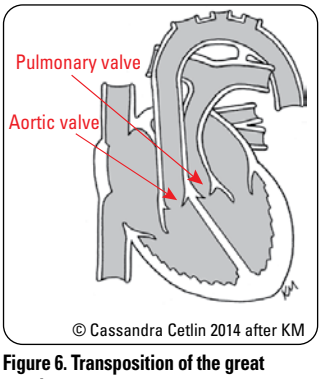



**Figure 6. Transposition of the great arteries**

### Total Anomalous Pulmonary Venous Return

- **epidemiology**: 1-2% of CHD
- **pathophysiology**
  - all pulmonary veins drain into right-sided circulation (systemic veins, RA)
  - no direct oxygenated pulmonary venous return to left atrium
  - often associated with obstruction at connection sites
  - ASD must be present for oxygenated blood to shunt into the LA and systemic circulation
- **management**: surgical repair in all cases and required urgently for severe cyanosis

**Ebstein's Anomaly**
- Septal and posterior leaflets of tricuspid valve are malformed and displaced into the RV
- Potential for RV dysfunction, tricuspid stenosis, tricuspid regurgitation, or functional pulmonary atresia if RV unable to open pulmonic valves
- Accessory conduction pathways (e.g. WPW) are often present

**Etiology**
- Unknown, associated with maternal lithium and benzodiazepine use in 1st trimester

**Treatment**
- Newborns: consider closure of tricuspid valve + aortopulmonary shunt, or transplantation
- Older children: tricuspid valve repair or valve replacement + ASD closure

### Truncus Arteriosus
- **pathophysiology**
  - single great vessel gives rise to the aorta, pulmonary, and coronary arteries
  - truncal valve overlies a large VSD
  - potential for coronary ischemia with fall in pulmonary vascular resistance
- **management**: surgical repair within first 6 wk of life

### Hypoplastic Left Heart Syndrome
- **epidemiology**: 1-3% of CHD; most common cause of death from CHD in first mo of life
- **pathophysiology**: LV hypoplasia may include atretic or stenotic mitral and/or aortic valve, small ascending aorta, and coarctation of the aorta with resultant systemic hypoperfusion
- systemic circulation is dependent on ductus patency; upon closure of the ductus, infant presents with circulatory shock and metabolic acidosis
- **management**
  - intubate and correct metabolic acidosis
  - IV infusion of prostaglandin E1 to keep ductus open
  - surgical palliation (overall survival 50% to late childhood) or heart transplant



**4 Features of Hypoplastic Left Heart Syndrome**
- Hypoplastic LV
- Narrow mitral/aortic valves
- Small ascending aorta
- Coarctation of the aorta

## Congestive Heart Failure

• see Cardiology and Cardiac Surgery, C34

### Etiology
- CHD
- cardiomyopathy (primary or secondary)
- high output circulatory states (e.g. anemia, AVMs, cor pulmonale, hyperthyroidism)
- non-cardiac (e.g. sepsis, renal failure)
- pressure overload (e.g. aortic stenosis/co-arctation, pulmonary stenosis, HTN)
- volume overload (e.g. L to R shunt, valve insufficiency)

### Clinical Features
- infant: weak cry, irritability, feeding difficulties, early fatigability, diaphoresis while sleeping or eating, respiratory distress, lethargy, FTT
- child: decreased exercise tolerance, fatigue, decreased appetite, respiratory distress, frequent URTIs or "asthma" episodes
- orthopnea, paroxysmal nocturnal dyspnea, pedal/dependent edema are all uncommon in children
- physical findings: 4 key features (tachycardia, tachypnea, cardiomegaly, hepatomegaly). Also FTT, alterations in peripheral pulses, four limb blood pressures (in some CHDs), dysmorphic features associated with congenital syndromes



**4 Key Features of CHF**

**2 Tachy's and 2 Megaly's**
- Tachycardia
- Tachypnea
- Cardiomegaly
- Hepatomegaly

### Investigations
- CXR: cardiomegaly, pulmonary venous congestion
- ECG: sinus tachycardia, signs of underlying cause (heart block, atrial enlargement, hypertrophy, ischemia/infarct)
- echo: structural and functional assessment
- blood work: CBC, electrolytes, BUN, Cr, LFTs

### Management
- general: sitting up, $O_2$, sodium and water restriction, increased caloric intake
- pharmacologic: diuretics, afterload reduction (e.g. ACEI), β-blockers; digoxin rarely used
- curative: correction of underlying cause

## Dysrhythmias

- can be transient or permanent, congenital (structurally normal or abnormal), or acquired (toxin, infection, infarction)

### Sinus Arrhythmia
- phasic variations with respiration (present in almost all normal children)

### Sinus Tachycardia
- rate of impulses arising from sinus node is elevated (>150 bpm in infants, >100 bpm in older children)
- characterized by: beat-to-beat heart rate variability with changes in activity, P waves present/normal, PR constant, QRS narrow
- etiology: HTN, fever, anxiety, sepsis, anemia/hypoxia, pain, PE, drugs, etc.
- differentiate from SVT by slowing the sinus rate (vagal massage, β-blockers) to identify sinus P waves

### Premature Atrial Contractions
- may be normal variant or can be caused by electrolyte disturbances, hyperthyroidism, cardiac surgery, digitalis toxicity



**Pediatric vs. Adult ECG**

Pediatric ECG findings that may be normal:
- HR >100 bpm
- Shorter PR and QT intervals and QRS duration
- Inferior and lateral small Q waves
- RV larger than LV in neonates, so normal to have:
  - RAD
  - Large precordial R waves
  - Upright T waves
  - Inverted T waves in the anterior precordial leads from early infancy to teen years

### Premature Ventricular Contractions
- common in adolescents
- benign if single, uniform, disappear with exercise, and no associated structural lesions
- if not benign, may degenerate into more severe dysrhythmias

### Supraventricular Tachycardia
- abnormally rapid heart rhythm originating above the ventricles – most frequent sustained dysrhythmia in children
- no beat-to-beat HR variability, >220 bpm (infants) or >180 bpm (children), P waves absent/abnormal, PR indeterminable, QRS usually narrow
- pre-excitation syndromes (subset of SVT): WPW syndrome, congenital defect (see Cardiology and Cardiac Surgery, C21)

### Complete Heart Block
- congenital heart block can be caused by maternal anti-Ro or anti-La (e.g. mother with SLE)
- often diagnosed *in utero* (may lead to development of fetal hydrops)
- clinical symptoms related to level of block (the lower the block, the slower the heart rate and greater the symptoms of inadequate cardiac output)
- symptomatic patients need a pacemaker

## Heart Murmurs



- 50-80% of children have audible heart murmurs at some point in their childhood
- most childhood murmurs are functional (e.g. "innocent") without associated structural abnormalities and have normal ECG and radiologic findings
- in general, murmurs can become audible or accentuated in high output states (e.g. fever, anemia)

**Table 12. Differentiating Heart Murmurs**

| | Innocent | Pathological |
|---|---|---|
| **History and Physical** | Asymptomatic | Symptoms and signs of cardiac disease (FTT, exercise intolerance) |
| **Timing** | SEM | All diastolic, pansystolic, or continuous (except venous hum) |
| **Grade/Quality** | <3/6; soft/blowing/vibratory | ≥3/6 (palpable thrill); harsh |
| **Splitting** | Physiologic S2 | May have fixed split or single S2 |
| **Extra Sounds/Clicks** | None | May be present |
| **Change of Position** | Murmur varies | Unchanged |

**Table 13. Five Innocent Heart Murmurs**

| Type | Etiology | Location | Description | Age | Differential Diagnosis |
|---|---|---|---|---|---|
| **Peripheral Pulmonic Stenosis** | Flow into pulmonary branch arteries from main, larger, artery | Left upper sternal border | Neonates, low-pitched, radiates to axilla and back | Neonates, usually disappears by 3-6 mo | PDA<br>Pulmonary stenosis |
| **Still's Murmur** | Flow across the pulmonic valve leaflets | Left lower sternal border | High-pitched, vibratory, LLSB or apex, SEM | 3-6 yr | Subaortic stenosis<br>Small VSD |
| **Venous Hum** | Altered flow in veins | Infraclavicular (R>L) | Infraclavicular hum, continuous, R>L | 3-6 yr | PDA |
| **Pulmonary Ejection** | Flow through the pulmonic valve | Left upper sternal border | Soft, blowing, LUSB, SEM | 8-14 yr | ASD<br>Pulmonary stenosis |
| **Supraclavicular Arterial Bruit** | Turbulent flow in the carotid arteries | Supraclavicular | Low intensity, above clavicles | Any age | Aortic stenosis<br>Bicuspid aortic valve |

## Infective Endocarditis

- see Infectious Diseases, ID13

# Development

## Approach to Global Developmental Delay

- also known as Early Developmental Impairment

### Definition
- significant delay (at least 2 SDs below the mean with standardized tests) in at least two developmental domains (gross motor, fine motor, speech/language, cognitive, social/personal, activities of daily living) in a child <5 yr of age
- predict a diagnosis of intellectual disability in the future
- after 5 years of age, intellectual and physical disabilities are described (no longer a development 'delay' as catch up is not expected

### Epidemiology
- 5-10% of children have neurodevelopmental delay
- careful evaluation can reveal a cause in 50-70% of cases

### Etiology

| Broad category | Possible causes | Upper limit of diagnostic yield* |
|---|---|---|
| **Prenatal Biological Factors** | Genetic mutations<br>Central nervous system deformities<br>Metabolic issues | 47%<br>28% |
| **Prenatal Environmental Factors** | Teratogens/toxins (substances of abuse, medications, etc.)<br>Infections | 21% |
| **Perinatal** | Asphyxia<br>Premature birth<br>Neonatal complications | 55% |
| **Postnatal** | Neglect/unhealthy psychosocial environment<br>Infections<br>Trauma<br>Toxins | 11% |

*Percentage of total cases of GDD or ID with an identified etiologic diagnosis who fall into this specific category

### Clinical Feature
- key questions in addition to standard pediatric history:
  - detailed developmental milestones: rate of acquisition, regression of skills
  - associated problems: feeding, seizures, behaviour, sleep
  - ototoxic antibiotics, frequent ear infections
- physical exam
  - micro/macrocephaly, dysmorphic features head-to-toe, hepatosplenomegaly, height and weight
  - **neurodevelopmental exam** (neurological exam, congenital abnormalities, dysmorphic features, current developmental level)
- investigations (guided by history and physical examination); see CPS step-wise algorithm
  - vision and hearing test
  - EEG if suspected seizures
  - chromosomal microarray, karyotype, Fragile X DNA testing,
  - brain MRI if abnormal neuro exams, micro/macroecephalopathy
  - MECP2 in girls with clinical course suggestive of Rett's Syndrome
  - metabolic screening (glucose, electrolytes, lactate, ammonia, liver function, pyruvate, albumin, trigylcerides, uric acid, amino acids, urine organic acids, acylcarnitine profile, carnitine (free and total), creatine phosphokinase, homocysteine, Biotinidase, copper, ceruloplasmin
  - lead, CBC, blood gas, urea, creatitine, electrolytes with anion gap, ferritin, B12, TSH, CK
  - OT, PT, and/or SLP assessments

### Management
- dependent on specific area of delay
- therapy services (e.g. speech and language therapy for language delay, OT and/or PT for motor delay), early intervention services (e.g. infant development services, Ontario Early Years Centres)

## Intellectual Disability

### Definition
- state of functioning that begins in childhood and is characterized by limitations in both intelligence and adaptive skills
- historically defined as an IQ <70
- often preceded by diagnosis of global developmental delay

### Epidemiology
- 1% of general population; M:F = 1.5:1

**Classification of Intellectual Disability**

| Severity | % Cases | IQ |
|---|---|---|
| Mild | 85 | 50-70 |
| Moderate | 10 | 35-49 |
| Severe | 3-4 | 20-34 |
| Profound | 1-2 | <20 |

### Clinical Feature
- history
  - earlier age of onset correlates with greater severity of ID
  - well below average general intellectual functioning
  - significant deficits in adaptive functioning in at least 2 of: communication, self-care, home-living, social skills, self-direction, academic skills, work, leisure, health, safety
- physical exam
  - check growth, dysmorphic features, complete physical exam
- investigations
  - standardized psychology assessment (includes IQ test and measure of adaptive functioning)
  - vision, hearing, and neurologic assessment
  - genetic and metabolic testing as indicated

### Management
- main objective: enhance adaptive functioning level
- requires an interprofessional team with strong case coordination
- emphasize community-based treatment and early intervention
- behaviour management services, therapy services (e.g. OT, SLP), medications for associated conditions
- education: life skills, vocational training, communication skills, family education
- psychosocial support for individual and family; respite care, individual/family therapy

### Prognosis
- higher rates of sensory deficits, motor impairment, behavioural/emotional disorders, seizures, psychiatric illness

## Language Delay

### Definition
- no universally accepted definition, but often identified around 18 mo of age with enhanced well baby visit
- if formally tested, at least one standard deviation below mean of age on standardized testing
- can be expressive (ability to produce or use language), receptive (ability to understand language), or both

### Epidemiology
- M>F
- ~10-15% of 2 yr old children have a language delay, but only 4-5% remain delayed after 3 yr of age
- ~6-8% of school-aged children have specific language impairment (many of whom were not identified before school entry)

### Etiology
- intellectual disability
- developmental disorders: cerebral palsy, autism spectrum disorder, constitutional language delay
  - constitutional language delay
- genetic/metabolic: DS, Fragile X syndrome, Williams syndrome, hypothyroidism, PKU, etc.
- mechanical problems: cleft palate, cranial nerve palsy, hearing impairment
- medical condition: seizure disorder (includes acquired epileptic aphasia), CP, TORCH infection, iron deficiency, lead poisoning, etc.
- psychosocial: neglect or abuse
- selective mutism
- language specific learning disorder
- isolated language delay

### Clinical Feature
- history
  - concerns about hearing, delay in language development or regression in previously normal language development
  - delayed language milestones, presence of red flags, regression (see Table 6, *Developmental Milestones*, P6)
  - must determine if language delay is expressive, receptive, or mixed
  - determine differences in behaviour at home, school, other social environments
  - risk factors: family history of speech and language delay, male, prematurity, low birth weight, hearing loss
- physical exam
  - guided by history: look for abnormal growth, dysmorphisms, unusual social interactions (lack of eye contact, not pointing)
  - include full exam of the external/internal ear (e.g. TM scarring), oral pharynx (e.g. cleft palate), and neurologic system (including tone)
- investigations
  - use of language specific screens in primary care setting: The Early Language Milestone
  - Clinical Adaptive Test/Clinical Linguistic and Auditory Milestone Scale (CAT/CLAMS), Modified Checklist for Autism in Toddlers (M-CHAT), etc.
  - developmental evaluation
  - hearing and vision screening (audiology and optometry referral)
  - CBC (to rule out anemia), venous blood lead levels, genetic/metabolic workup as indicated



**Risk Factors for Sensorineural Hearing Loss**
- Genetic syndromes/family history
- Congenital (TORCH) infections
- Craniofacial abnormalties
- <1500 g birthweight
- Hyperbilirubinemia/kernicterus
- Asphyxia/low APGAR scores
- Bacterial meningitis, viral encephalitis



Bilingual exposure generally does NOT explain a frank delay in language development



Primary care physicians should suspect a receptive language delay in any young child with an expressive language delay

### Management
- specific to etiology
- referrals to: SLP, Otolaryngology Head and Neck Surgery (OHNS), and dental professionals, general support services
- prevention: parents can read aloud to their child, engage in dialogic reading, avoid baby talk, narrate daily activities, etc.

### Prognosis
- depends on etiology – best prognosis for developmental speech delay
- if language delay persists beyond 5 yr old, more likely to have difficulties in adulthood
- persistent language delay is associated with poor academic performance, behavioural problems, social isolation

## Specific Learning Disorder

### Definition
- specific and persistent failure to acquire academic skills despite conventional instruction, adequate intelligence, and sociocultural opportunity
- a significant discrepancy between a child's intellectual ability and their academic performance
- types: reading (dyslexia), writing, mathematics (dyscalculia)

### Epidemiology
- prevalence: 10%
- high incidence of psychiatric comorbidity: anxiety, dysthymia, conduct disorder, major depressive disorder, oppositional defiant disorder, ADHD

### Etiology
- pathogenesis is unknown, likely genetic factors involved
- learning disabilities may be associated with a number of conditions:
  - genetic/metabolic: Turner syndrome, Klinefelter syndrome
  - perinatal: prematurity, low birth weight, birth trauma/hypoxia
  - postnatal: CNS damage, hypoxia, environmental toxins, FAS, psychosocial deprivation (understimulation), malnutrition
- poor visual acuity is NOT a cause

### Risk Factors
- positive family history, prematurity, other developmental and mental health conditions, neurologic disorders (e.g. seizure disorders, neurofibromatosis), history of CNS infection/irradiation/traumatic injury

### Clinical Feature
- history and physical exam
  - school difficulties (academic achievement, behaviour, attention, social interaction, over-reliance on teacher)
  - development of negative self-concept → reluctance to participate even in areas of strength
  - social issues: overt hostility towards parents/teachers; difficulties making friends, bullying, and anxiety
  - look for dysmorphisms, complete physical exam
- investigations
  - psychoeducational assessment, educational history from school staff
  - individual scores on achievement tests in reading, mathematics, or written expression (WISC III, WRAT) >2 SD below that expected for age, education, and IQ
  - evaluate attention, memory, expressive language, coordination skills

### Management
- provide quality instruction for specific learning disability
- support student by modifying the curriculum and/or providing accommodations (e.g. scribe for writing, extra time for tests, photocopied notes, etc.)
- consider grade retention in certain students (no guidelines exist, very rare in Ontario)
- specialized education placements that can provide educational remediation

### Prognosis
- limited information available about persistence of learning disabilities over time
- low self-esteem, poor social skills, 40% school drop-out rate

## Fetal Alcohol Spectrum Disorder



### Definition
- term describing the range of effects of prenatal exposure to alcohol, including physical, mental, behavioural, and learning disabilities
- abstinence from alcohol during pregnancy is recommended
- spectrum includes: FAS, partial FAS, ARBD (alcohol related brain damage) and ARND (alcohol related neurodevelopmental disorder)

### Epidemiology
- prevalence of FAS and FASD is 0.1% and 1.0%, respectively
- most common preventable cause of intellectual disability

### Pathogenesis
- specific mechanism of FASD is unknown, but hypotheses include nutritional deficits, toxic effects of acetaldehyde, alteration of placental transport, abnormal protein synthesis, and altered cerebral neurotransmission

### Diagnosis
- often misdiagnosed or missed entirely
- diagnosis of FAS, ARBD, and ARND all require evidence of maternal drinking during pregnancy
- criteria for diagnosis of FAS
  - **growth deficiency**: low birth weight and/or decelerating weight over time not due to nutrition
  - **characteristic pattern of facial anomalies**: short palpebral fissures (<2 SD below mean), flattened philtrum, thin upper lip (having all 3 features is highly specific for alcohol exposure, don't need maternal history to confirm)
  - **CNS dysfunction (need ≥3)**: motor skills; neuroanatomy/neurophysiology; cognition; language; academic achievement; memory; attention; executive function (impulse control and hyperactivity); affect regulation; adaptive behaviour, social skills or social communication OR microcephaly in infant and young children
- criteria for diagnosis of ARBD
  - congenital anomalies, including malformations and dysplasias of the cardiac, skeletal, renal, ocular, and auditory systems
- criteria for diagnosis of ARND
  - CNS dysfunction (similar to FAS)
  - complex pattern of behavioural or cognitive abnormalities inconsistent with developmental level that cannot be explained by familial background or environment alone

### Management
- early diagnosis is essential to prevent secondary disabilities
- no cure, but individuals with FASD and their families should be linked to community resources and services to improve outcome

### Prognosis
- secondary disabilities include unemployment, mental health problems, difficulties with the law, inappropriate sexual behaviour, disrupted school experience, peer problems

## Attention Deficit Hyperactivity Disorder

- see Psychiatry, *Neurodevelopmental Disorders*, PS40

## Autism Spectrum Disorder

- see Psychiatry, *Neurodevelopmental Disorders*, PS40

## Motor Delay

- see *Cerebral Palsy*, P77 and Medical Genetics, *Duchenne Muscular Dystrophy*, MG8

# Endocrinology



## Antidiuretic Hormone

### Diabetes Insipidus
- see Endocrinology, E19 and Nephrology, NP11

### Syndrome of Inappropriate Antidiuretic Hormone
- see Endocrinology, E19 and Nephrology, NP10

## Diabetes Mellitus

### DIABETES MELLITUS TYPE 1
- see Endocrinology, E7

## Epidemiology
- most common form of DM in children, M=F
- variable prevalence internationally, affects ~1:4000 children in Canada
- can present at any age, but bimodal peaks at 5-7 yr old and at puberty

## Clinical Feature
- can present as polyuria (often manifested as nocturia or secondary enuresis), polydipsia, weight loss (lack of insulin leading to a catabolic state), polyphagia, DKA (~20%)

## Management
- patients and families are best managed with a family-centred pediatric multidisciplinary team able to provide education, ongoing care, and psychosocial support surrounding survival skills, meal plans, and insulin injections as a cornerstone of treatment
  - diet with consistent levels of carbohydrates, avoiding foods with high glycemic index is advised
  - exercise recommended, extensive activity may cause prolonged hypoglycemia
  - administer influenza immunization yearly to avoid complications to management
- blood glucose monitoring is especially important in children as they are more susceptible to hypoglycemia
  - administer glucagon or dextrose for severe hypoglycemia
- if DKA present: ABCs, 100% $O_2$, admit, monitor, correct fluid losses, conduct ECG (assess for abnormal T waves), administer insulin and restore glucose gradually (first SC and then IV if no improvement), correct electrolyte disturbances, identify/treat precipitating event, avoid complications (i.e. cerebral edema)
  - low threshold to investigate (CT/MRI) and treat DKA, as cerebral edema is a major concern
    - signs of neurological deterioration – headache, bradycardia, irritability, decrease LOC, incontinence, specific neurological signs
    - administer mannitol for cerebral edema
  - frequent BG, fluid and electrolyte monitoring
  - see Endocrinology, E12
- screen for micro- and macrovascular complications (regular ophthalmology assessments, BP, microalbuminuria), concurrent autoimmune diseases (thyroiditis, celiac disease, etc.), and mental health issues (depression, eating disorders), hypertension, dyslipidemia

## Prognosis
- no cure currently
- short-term complications
  - hypoglycemia
    - due to missed/delayed meals, excess insulin or exercise, illness
    - can lead to seizures and/or coma
    - reversed with PO/IV glucose or IM glucagon
  - hyperglycemia
    - due to intercurrent illness, diet-to-insulin mismatch
    - risk of end-organ damage
  - DKA: due to missed insulin doses, infection; most common cause of death
- long-term complications
  - microvascular: retinopathy, nephropathy, neuropathy
  - macrovascular: metabolic syndrome, CVD, CAD, PVD
  - increased risk of other autoimmune diseases
  - hypertension, dyslipidemia

## DIABETES MELLITUS TYPE 2
- see Family Medicine, FM22, and Endocrinology, E7
- impaired glucose metabolism due to increased peripheral insulin resistance
- rare before 10 yr of age, but more common in older children/adolescents
- prevalence is rising mainly due to the increased incidence of childhood obesity
- risk factors: obesity, positive family history, female gender, PCOS, hyperglycemia exposure in utero, certain ethnic groups
  - risk reduced with breastfeeding
- clinical feature may be similar to that of type 1 DM, though most children are asymptomatic
- may present in DKA or hyperglycemic hyperosmotic nonketotic state
  - investigation – fasting plasma glucose recommended, oral glucose tolerance test for very obese children with multiple risk factors
- management
  - insulin used for severe metabolic decompensation at diagnosis (DKA, A1C >9%), can wean off
  - initiate lifestyle modification program, including diet, weight loss, physical activity (moderate-to-vigorous activity for at least 60 min/d; screen time less than 2 h/d)
  - glycemic target: HbA1c ≤7%
  - if glycemic targets not achieved within 3-6 mo from diagnosis with lifestyle intervention alone, either metformin (first line), glimepiride, or insulin should be initiated
    - metformin can be initiated at diagnosis if HbA1c >7%
  - monitor HbA1c every 3 mo
  - advise patient to monitor finger-stick blood glucose levels if on medication with risk of hypoglycemia, are changing medication regimen, have not met treatment goals, or have intercurrent illness
  - screening – same as T1D plus annual screening for polycystic ovary syndrome (PCOS) and nonalcoholic fatty liver disease (NAFLD)
- prognosis: includes microvascular and macrovascular complications similar to type 1 DM



**Diagnostic Criteria for DM (Types 1 and 2) in Children**

1. Symptoms (polyuria, polydipsia, weight loss, etc.) and hyperglycemia (Random glucose ≥11.1 mmol/L)

**OR**

2. Two of the following on one occasion:
- Fasting glucose ≥7.0 mmol/L
- 2 h plasma glucose during OGTT ≥11.1 mmol/L
- Random glucose ≥11.1 mmol/L (not appropriate for confirmatory testing)

**OR**

3. One of the following on two separate occasions*
- Fasting glucose ≥7.0 mmol/L
- 2 h plasma glucose during OGTT ≥11.1 mmol/L
- Random glucose ≥11.1 mmol/L (not appropriate for confirmatory testing)

*Random glucose is not appropriate for confirmatory (second) testing



**Blood Glucose Targets by Age**

| Age range | Pre-meal blood glucose target | HbA1c target |
|---|---|---|
| <6 | 6-10 | <8% |
| 6-12 | 6-10 | <7.5% |
| >12 | 4-7 | <7% |



**Management of Newly Diagnosed Type 2 DM in Children and Adolescents**

Pediatrics 2013;131(2):364-82

**Key Action Statements**

1. Clinicians should ensure that insulin therapy is initiated for children and adolescents with type 2 DM who are ketotic or in DKA and in whom the distinction between types 1 and 2 DM is unclear and, in usual cases, should initiate insulin therapy for patients
   a. who have random venous or plasma BG concentrations 14 mmol/L; or
   b. whose HbA1c is >9%.
2. Clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of type 2 DM.
3. The committee suggests that clinicians monitor HbA1c concentrations every 3 mo and intensify treatment if treatment goals for finger-stick BG and HbA1c concentrations are not being met.
4. Clinicians should advise patients to monitor finger-stick BG concentrations in patients who
   a. are taking insulin or other medications with a risk of hypoglycemia; or
   b. are initiating or changing their diabetes treatment regimen; or
   c. have not met treatment goals; or
   d. have intercurrent illnesses.
5. Clinicians should incorporate the Academy of Nutrition and Dietetics' Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines in their dietary or nutrition counselling of patients with type 2 DM at the time of diagnosis and as part of ongoing management.
6. Clinicians should encourage children and adolescents with type 2 DM to engage in moderate-to-vigorous exercise for at least 60 min daily and to limit nonacademic "screen time" to less than 2 h/d.

# Growth (see Failure to Thrive)

## APPROACH TO SHORT STATURE

### Definition
- short stature: height <3rd percentile
- poor growth evidenced by growth deceleration (height crosses major percentile lines, growth velocity <25th percentile)

### Epidemiology
- ~2.5% of the population by definition

### Etiology
- see sidebar

### Clinical Feature
- history and physical exam
  - plot on growth curve (special growth charts available for Turner syndrome, achondroplasia, DS)
  - assess for dysmorphic features, disproportionate short stature
  - risk factors for GH deficiency: previous head trauma, history of intracranial bleed or infection, head surgery or irradiation, positive family history, breech delivery
  - decreased growth velocity may be more worrisome than actual height
- investigations
  - calculate mid-parental height: children are usually in a percentile between their parents' height (mid-parental height = (mother + father's height in cm ± 12.5cm)/2)
  - AP x-ray of left hand and wrist for bone age
  - GH testing
  - remaining investigations guided by history and physical (e.g. TSH, sweat chloride, etc.)

### Management
- depends on severity of problem as perceived by parents/child
- no treatment for non-pathological short stature, except for idiopathic short stature
- GH therapy for GH deficiency: if administered at an early age, can help patients achieve adult height
- requirements
  - GH shown to be deficient by 2 different stimulation tests (with arginine, glucagon, insulin)
  - growth velocity <3rd percentile or height <<3rd percentile
  - bone age x-rays show unfused epiphyses/delayed bone age
- support and management of resultant self-image issues, social anxiety, etc.

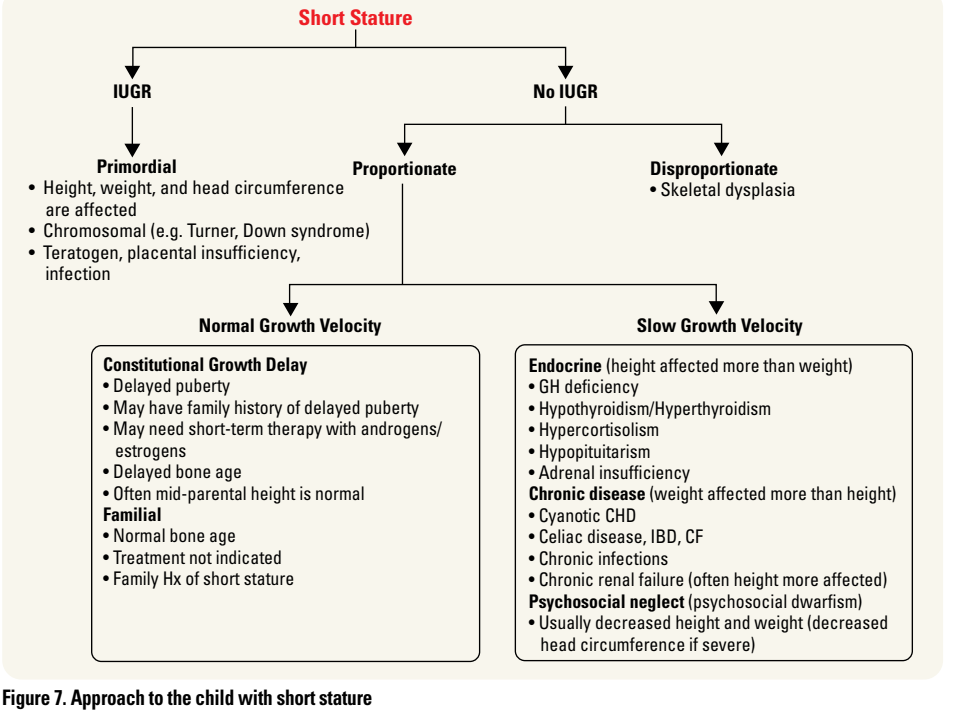



**Figure 7. Approach to the child with short stature**

**Short Stature DDx**

**ABCDEFG**
**A**lone (neglected infant)
**B**one dysplasias (rickets, scoliosis, mucopolysaccharidoses)
**C**hromosomal (Turner, Down)
**D**elayed growth (constitutional)
**E**ndocrine (low GH, Cushing, hypothyroid)
**F**amilial
**G**I malabsorption (celiac, Crohn's)

**4 Questions to Ask when Evaluating Short Stature**
- Was there IUGR?
- Is the growth proportionate?
- Is the growth velocity normal?
- Is bone age delayed?

To check for proportionality, measure upper to lower segment ratio (U/L) using the pubic symphysis as your landmark. Normals are 1.7 for newborn, 1.4 for young child, 0.9 for adult male, 1.0 for adult female

### TALL STATURE
- height greater than two SD above the mean for a given age, sex, and race

#### Etiology
- constitutional/familial
- endocrine: Beckwith-Wiedemann syndrome, hyperthyroidism, hypophyseal gigantism, precocious puberty
- genetic: homocystinuria, Klinefelter syndrome, Marfan syndrome, Sotos syndrome

## Hypercalcemia/Hypocalcemia/Rickets

- see Endocrinology, E40, E41, E45

## Hyperthyroidism and Hypothyroidism

- may be congenital or acquired (for acquired causes, see Endocrinology, E27)

### CONGENITAL HYPERTHYROIDISM
- also known as neonatal Graves' disease

#### Epidemiology
- ~1:25,000 neonates, M=F

#### Etiology
- typically caused by transplacental transfer of TSH receptor antibody
- rare causes include mutations in the TSH receptor pathway

#### Clinical Feature
- history and physical exam
  - maternal history of thyroid pathology and management
  - low birthweight, IUGR, microcephaly, premature birth, tachycardia, irritability, frontal bossing, triangular facies, hepatosplenomegaly, goitre

#### Investigations
- TSH receptor antibody levels during the 3rd trimester or in the cord blood
- neonatal TSH, T3, free T4

#### Management
- methimazole and β-adrenergic blocker (E.g. propranolol)

#### Prognosis
- with prompt treatment, hyperthyroidism improves
  - however, long-term cognitive and CNS problems can still occur
- risk for development of central hypothyroidism later in life

### CONGENITAL HYPOTHYROIDISM

#### Epidemiology
- incidence: 1:4000-1:20,000 newborn births; F:M = 2:1
- one of the most common preventable causes of intellectual disability

#### Etiology
- may be classified as permanent or transient congenital hypothyroidism (CH)
  - subcategorize into primary (85% dysgenesis, 15% thyroid gland disorder), secondary/central (pituitary/hypothalamic issue), or peripheral CH (deficits in thyroid hormone transport, metabolism or action)
  - permanent CH requires lifelong treatment, transient CH recovers to normal thyroid after neonatal period
- causes of transient hypothyroidism: maternal - antibody-mediated, iodine deficiency (rare in developed countries), prenatal exposure to antithyroid medications; neonatal – neonatal iodine deficiency/excess, congenital liver hemangiomas, certain gene mutations

#### Clinical Feature
- history and physical exam
  - usually asymptomatic in neonatal period because maternal T4 crosses the placenta
  - prolonged jaundice, feeding difficulty, lethargy, constipation, umbilical hernia, macroglossia, large fontanelles, puffy face, swollen eyes
  - examine for congenital malformations (especially cardiac) and dysmorphic features
  - most commonly presents as a positive newborn screen result

- investigations
  - screen all infants for primary CH
  - repeat screening at 2 wk for infants at high risk: preterm, (very)-low birth weight, infants in NICU, specimen collection <24 h of life, multiple births
  - diagnosis through newborn screening of TSH (most sensitive for primary CH) or free T4; abnormal results should be confirmed with serum levels from venipuncture
    - ↑ TSH, ↓ free T4 in primary CH
    - ↓ TSH, ↓ free T4 in secondary CH
  - primary CH (optional): radioisotope scanning/ultrasound of thyroid for severity, serum thyroglobulin, maternal antithyroid antibodies, urinary iodine
  - secondary CH: MRI, gene analysis, eye exam for optic nerve hypoplasia (assess pituitary)

### Management
- thyroxine replacement, hormone normalization should be done within 2 wk to avoid cognitive impairment

### Prognosis
- excellent outcome if treatment started within 1-2 mo of birth
- if treatment started after 3-6 mo of age, may result in permanent developmental delay and/or disability (mild to profound), intellectual impairment, poor growth, hearing loss

# Disorders of Sexual Development

## AMBIGUOUS GENITALIA

### Definition
- newborn or child whose gender is difficult to assign based on the appearance of genitalia
- subtype of DSD: a condition in which development of chromosomal, gonadal, or anatomic sex is atypical
- subtypes: 46,XX DSD, 46,XY DSD, ovotesticular DSD (true hermaphrodite)

### Epidemiology
- incidence of genital abnormalities at birth is as high as 1:300
- prevalence of complex anomalies with true sexual ambiguity much lower at ~1:5000

### Etiology
- 46,XY DSD
  - inborn error of testosterone biosynthesis or Leydig cell hypoplasia
  - 5-α-reductase deficiency, androgen receptor deficiency or insensitivity
  - LH/hCG unresponsiveness
- 46,XX DSD
  - virilizing CAH (most common)
  - maternal source: virilizing ovarian or adrenal tumours, untreated maternal CAH, placental aromatase deficiency
- ovotesticular DSD
  - both ovarian follicles and seminiferous tubules in the same patient with a 46,XX karyotype
  - mixed gonadal dysgenesis

### Risk Factors
- parental consanguinity, positive family history of ambiguous genitalia, early childhood illness/death, or primary amenorrhea, maternal medications during pregnancy (e.g. androgens, progesterones, danazol, phenytoin, aminoglutethimide, endocrine disruptors)

### Clinical Feature
- history
  - thorough obstetrical history, including prenatal screens and maternal medications
  - family history: autosomal recessive pattern may suggest CAH, X-linked recessive pattern may suggest androgen insensitivity syndrome
- physical exam
  - male pseudohermaphrodite (XY): small phallus, hypospadias, undescended testicles
  - female pseudohermaphrodite (XX): clitoral hypertrophy, labioscrotal fusion
  - look for concurrent midline defects, dysmorphic features, and congenital abnormalities
- investigations
  - karyotype and genetic workup as indicated
  - blood work: electrolytes and renin (evidence of salt-wasting in CAH); 17-OH-progesterone, androgens, FSH, and LH
  - imaging: abdominal U/S to look for uterus, testicles, ovaries

### Management
- avoid announcement of probable sex or use of personal pronouns until all tests are complete
- continuous psychosocial support for parents and child during development
- elective surgical reconstruction of genitalia is sometimes possible

## CONGENITAL ADRENAL HYPERPLASIA

### Definition
- autosomal recessive disorder characterized by the partial or total defect of various synthetic enzymes required for cortisol and aldosterone production in the adrenal cortex
  - adrenal cortex normally produces balanced levels of aldosterone, cortisal and androgens

### Epidemiology
- occurs in ~1:15,000 live births
- most common cause of ambiguous genitalia in genotypically normal females (46XX)

### Etiology
- for biosynthetic pathways of adrenal cortex
- 21-OH responsible for ~95% of CAH cases
- results in ↓ cortisol and aldosterone production with shunting toward ↑↑ androgens
- cortisol deficiency leads to elevated ACTH, which causes adrenal hyperplasia
- rarer causes include deficiencies in 11-OH, cholesterol desmolase, 17-OH, and 3-HSD

### Clinical Feature
- depends on which enzyme in cortisol synthesis pathway is defective
- presentation of 21-OH deficiency can be divided into:
  - classic deficiency with salt wasting: inadequate aldosterone resulting in FTT, hyperkalemia, hyponatremia, hypoglycemia, acidosis (majority of classic CAH types)
  - classic deficiency without salt wasting: simple virilization with adequate aldosterone levels
    - females typically present with amenorrhea, precocious puberty, polycystic ovaries, hirsutism
    - males typically asymptomatic at birth, may show hyperpigmentation (from overproduction of melanocyte stimulating hormone), penile enlargement, rapid growth and accelerated skeletal maturation; present with signs of virilization later in life
  - non-classic CAH – mild androgen excess, sometimes asymptomatic, virilization present later in life, rarely associated with Addisonian crises
- 21-OH deficiency screening is part of many newborn screening programs across North America
- high serum levels of 17-OH progesterone in random blood sample diagnostic for 21-OH deficiency
  - assess plasma ACTH, serum electrolytes, plasma glucose, plasma aldosterone, plasma renin activity, blood gas
  - ultrasound – look for enlarged adrenal gland and presence of uterus

### Management
- correct any abnormalities in fluids, electrolytes, or serum glucose
- provide glucocorticoids (e.g. hydrocortisone)/mineralocorticoids (fludrocortisone) as necessary to reduce ACTH levels, extra glucocorticoids in times of stress
- psychosocial support

### Prognosis
- complications if untreated include virilization, acne, salt wasting, hypotension

## NORMAL PUBERTAL DEVELOPMENT

### Physiology
- puberty occurs with the maturation of the HPG axis
- ↑ pulsatile release of GnRH → ↑ release of LH and FSH → maturation of gonads, release of sex steroids → secondary sexual characteristics
- adrenal production of androgens also required

### Females
- onset: age 8-13 yr old (may start as early as 7 yr in girls of African descent)
- usual sequence
  1. thelarche: breast budding
  2. pubarche: axillary hair, body odour, mild acne
  3. growth spurt
  4. menarche: mean age 12.5 yr; indicates that growth spurt is almost complete; menses may be irregular in duration and length of cycle
- early puberty is common and often constitutional, late puberty is rare (rule out organic causes)

### Males
- onset: age 9-14 yr old
- usual sequence
  1. testicular enlargement
  2. penile enlargement
  3. pubarche: axillary and facial hair, body odour, mild acne
  4. growth spurt: occurs later in boys
- early puberty is uncommon (rule out organic causes), late puberty is common and often constitutional
- gynecomastia (transient development of breast tissue) is a common self-limited condition seen in 50% of males during puberty (but any discharge from nipple or fixed mass should be investigated)

### Tanner Staging
- scale used in pediatrics that defines physical measurements of development based on external primary and secondary sex characteristics

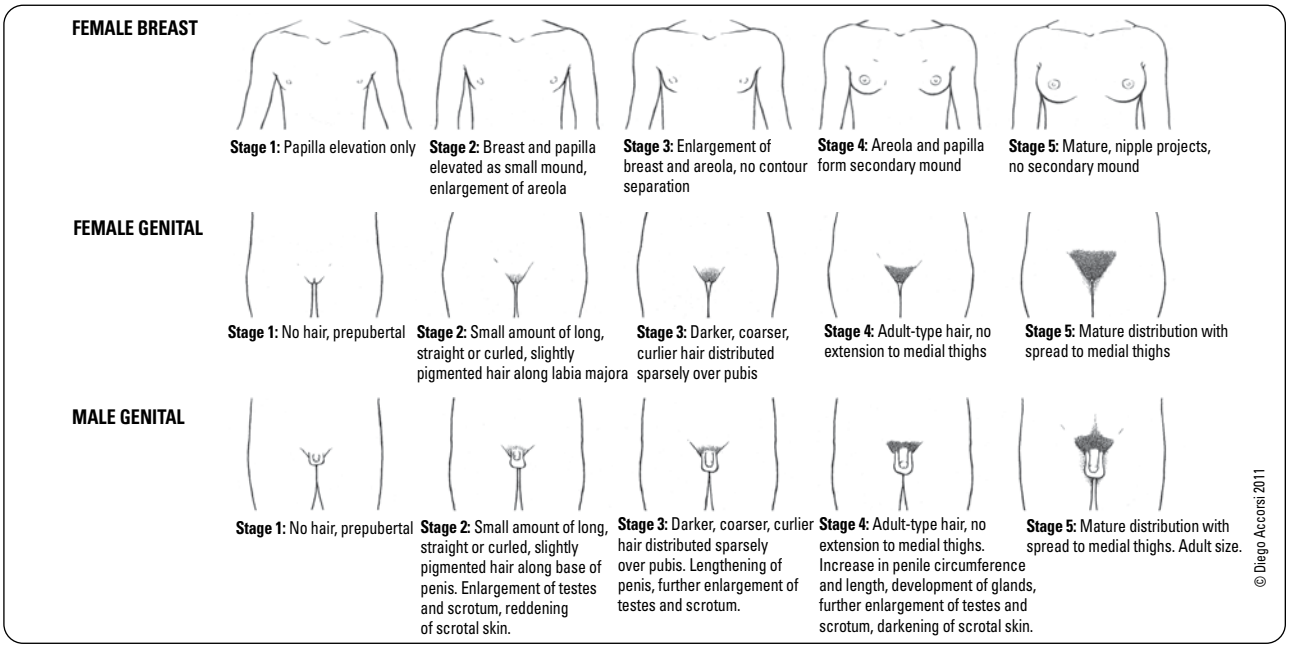



**Figure 8. Tanner staging**

## PRECOCIOUS PUBERTY

### Definition
- development of secondary sexual characteristics 2-2.5 SD before population mean
- <8 yr old for females, <9 yr old for males

### Epidemiology
- 1/10,000; F>M

### Etiology
- usually idiopathic in females (90%), more suggestive of pathology in males (50%)
- central (GnRH dependent)
  - hypergonadotropic hypergonadism; hormone levels as in normal puberty
  - premature activation of the HPG axis
  - differential diagnosis: idiopathic or constitutional (most common in females), CNS disturbances (tumours, hamartomas, post-meningitis, increased ICP, radiotherapy), NF, primary severe hypothyroidism
- peripheral (GnRH independent)
  - hypogonadotropic hypergonadism
  - differential diagnosis: adrenal disorders (CAH, adrenal neoplasm), testicular/ovarian tumour, gonadotropin/hCG secreting tumour (hepatoblastoma, intracranial teratoma, germinoma), exogenous steroid administration, McCune-Albright syndrome, aromatase excess syndrome, rarely hypothyroidism (Van Wyk-Grumbach syndrome), primary severe hypothyroidism

### Clinical Feature
- history
  - symptoms of puberty, family history of precocious puberty, medical illness
- physical exam
  - growth velocity
    - prepubertal: 4 to 6 cm/yr
    - growth spurt: boys 8-10 cm/yr, girls 6-8 cm/yr
  - complete physical exam, including Tanner staging and neurological assessment
- investigations
  - initial screening tests: bone age, serum hormone levels (estradiol, testosterone, LH, FSH, TSH, free T4, DHEA-S, 17-OH-progesterone)
  - secondary tests: MRI head, pelvic U/S, β-hCG, GnRH, and/or ACTH stimulation test



A child with proven central precocious puberty should receive an MRI of the brain

### Management
- indications for medical intervention to delay progression of puberty: rapid advancement of puberty, early age, risk of compromise of final adult height, psychological
- central causes: goals are to preserve height and alleviate psychosocial stress; GnRH agonists (e.g. leuprolide) most effective
- peripheral causes: goal is to limit effects of elevated sex steroids; treat underlying cause; medications that decrease the production of a specific sex steroid or block its effects (e.g. ketoconazole, spironolactone, tamoxifen, anastrozole), surgical intervention

## DELAYED PUBERTY

### Definition
- failure to develop secondary sex characteristics by 2-2.5 SD beyond the population mean
  - for males: lack of testicular enlargement by 14 yr old
  - for females: lack of breast development by 13 yr old OR absence of menarche by 16 yr old or within 5 yr of pubertal onset

### Epidemiology
- M>F

### Etiology
- usually constitutional delay in males, more suggestive of pathology in females
- central causes
  - constitutional delay in activation of HPG axis (most common)
  - hypogonadotropic hypogonadism
- peripheral causes
  - hypergonadotropic hypogonadism (e.g. primary gonadal failure, gonadal damage, Turner syndrome, hormone deficiency, androgen insensitivity syndrome, etc.)

### Clinical Feature
- history: weight loss, short stature, family history of puberty onset, medical illness, high performance athletes (females)
- physical exam: growth velocity (minimum 4 cm/yr), Tanner staging, neurological exam, complete physical exam
- investigations
  - initial screening tests: bone age, serum hormone levels (estradiol, testosterone, LH, FSH, TSH, free T4, IGF-1), CBC, electrolytes, BUN, Cr, LFTs, liver enzymes, ESR, CRP, urinalysis
  - secondary tests: MRI head, pelvic U/S, karyotype, IBD panel, celiac disease panel, LH levels following GnRH agonist

### Management
- identify and treat underlying cause
- hormonal replacement: cyclic estradiol and progesterone for females, testosterone for males

# Fluids and Electrolytes

## Approach to Infant/Child with Dehydration

### Etiology
- decreased intake: poor oral intake during acute illness, breastfeeding difficulties, eating disorders
- increased losses: common sites include GI tract (diarrhea, vomiting, bleeding), skin/mucous membranes (fever, burns, hemorrhage, stomatitis), urine (osmotic diuresis [e.g. hyperglycemia, DKA], diuretic therapy, DI, post-obstructive/post ATN recovery diuresis), and respiratory tract (tachypnea, bronchiolitis, pneumonia)

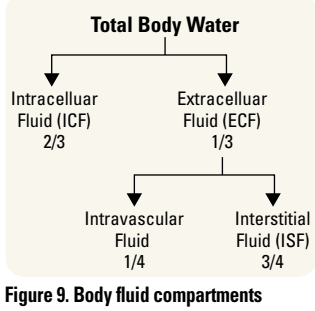



**Figure 9. Body fluid compartments**

### Management
- if suspect dehydration based on history (acute illness, decreased number of wet diapers, lethargy, changes in mental status, increased thirst, etc.), you must:

#### 1) Determine degree of extracellular volume contraction

**Table 14. Assessment of Degree of Extracellular Volume Contraction Based on Physical Exam**

| | Mild | Moderate | Severe |
|---|---|---|---|
| **<2 yr** | 5%* | 10%* | 15%* |
| **>2 yr** | 3%* | 6%* | 9%* |
| **Pulse** | Normal, full | Rapid | Rapid, weak |
| **Blood Pressure** | Normal | Low to normal | Decreased in shock (very late finding in pediatrics and very dangerous) |
| **Urine Output** | Decreased | Markedly decreased | Anuria |
| **Oral Mucosa** | Slightly dry | Dry | Parched |
| **Anterior Fontanelle** | Normal | Sunken | Markedly sunken |
| **Eyes** | Normal | Sunken | Markedly sunken |
| **Skin Turgor** | Normal | Decreased | Tenting |
| **Capillary Refill** | Normal (<3 s) | Normal to increased | Increased (>3 s) |

* Note that percentages refer to percent loss of pre-illness body weight

**Assessment of Severity of Dehydration**

**C BASE H$_2$0**
**C**apillary refill
**BP**
**A**nterior fontanelle
**S**kin turgor
**E**yes sunken
**HR**
**O**ral mucosa
**O**utput of urine

#### 2) Determine the likely electrolyte disturbance
- dependent on etiology of dehydration and type of fluid loss (isotonic vs. hypertonic vs. hypotonic)

**Table 15. Electrolyte Content of Various Bodily Fluids**

| Bodily Fluid | $Na^+$ (mmol/L) | $K^+$ (mmol/L) | $Cl^-$ (mmol/L) | $HCO_3^-$ (mmol/L) |
|---|---|---|---|---|
| Saliva | 30-80 | 20 | 70 | 30 |
| Gastric Juice | 60-80 | 15 | 100 | 0 |
| Pancreatic Juice | 140 | 5-10 | 60-90 | 40-100 |
| Bile | 140 | 5-10 | 100 | 40 |
| Small Bowel | 140 | 20 | 100 | 25-50 |
| Large Bowel | 75 | 30 | 30 | 0 |
| Sweat | 20-70 | 5-10 | 40-60 | 0 |

- for moderate and severe dehydration, initial investigations should include urinalysis and blood work examining electrolyte ($Na^+$, $K^+$, $Cl^-$), glucose, and acid-base (blood pH, $pCO_2$, $HCO_3^-$ disturbances), and impaired renal function (creatinine, BUN)

### 3) Determine if the child requires PO or IV rehydration

- dehydrated child must receive adequate fluid management, including replacement of ongoing losses and maintenance fluids
- ORT indication: mild to moderate dehydration
  - advantages: ↓ cost, no IV needed, no increase in incidence of iatrogenic hyper/hyponatremia, parental involvement in therapy
- indications for IV rehydration therapy: severe dehydration requiring close monitoring and frequent assessment of electrolytes, inability to tolerate ORT (e.g. vomiting, alteration in mental status, ileus, monosaccharide malabsorption, etc.), inability to provide ORT, failure of ORT in providing adequate rehydration (e.g. persistent diarrhea or vomiting)

### 4) Return the child to a normal volume and electrolyte status by replacing current deficits and ongoing losses

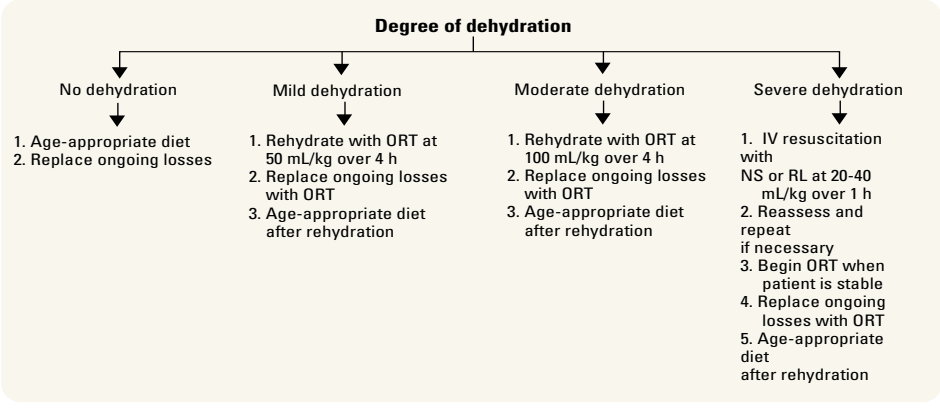



**Figure 10. Algorithm for deficit replacement and replacement of ongoing losses in the dehydrated child**

**Special Consideration – SIADH**
**Clinical Signs:** hyponatremia and excretion of concentrated urine
**Risk Factors:** certain medications (e.g. morphine), post-operative, pain, N/V, pulmonary disease (e.g. pneumonia), CNS disease (e.g. meningitis)
**Caution:** acute hyponatremia is associated with rapid administration of hypotonic IV fluids, this can lead to cerebral edema and brain herniation or central pontine myelinolysis

### 5) Provide the appropriate fluid and electrolyte maintenance daily requirements

**Table 16. Maintenance Fluid Requirements**

| Body Weight | 100:50:20 Rule (24 h maintenance fluids) | 4:2:1 Rule (hourly rate of maintenance fluids) |
|---|---|---|
| 1-10 kg | 100 cc/kg/d | 4 cc/kg/h |
| 11-20 kg | 1000 cc + 50 cc/kg/d for every kg >10 kg | 40 cc + 2 cc/kg/h for every kg >10 kg |
| >20 kg | 1500 cc + 20 cc/kg/d for every kg >20 kg | 60 cc + 1 cc/kg/h for every kg >20 kg |

- in children, all maintenance fluids should have a dextrose component due to their higher risk of hypoglycemia, especially if they are NPO
- common IV fluid combinations used in pediatrics
  - newborn: D10W
  - 1st mo of life: D5W/0.45 2 NS + KCl 20 mEq/L (only add KCl if voiding well)
  - children
  - without special considerations:
    - D5W/NS + KCl 20 mEq/L – decreased risk of hyponatremia
    - NS bolus for dehydration
  - other options: D5W0.45%NS + KCl 20 mEq/L
- most important thing to remember when correcting $Na^+$ aberrations due to fluid deficits
  - risk of cerebral edema with rapid rehydration with hypotonic or isotonic solutions (i.e. NS)
    - therefore replace fluid slowly with close monitoring
    - aim to adjust (increase or decrease) plasma [$Na^+$] by no more than 12 mmol/L/d
- management depends on etiology, severity of symptoms, and timing (acute vs. chronic)

### 6) Continue to monitor fluid and electrolyte status
- accurate monitoring of daily fluid intake (PO and IV) and ongoing losses (urine output, diarrhea, emesis, drains)
- if child receiving >50% of maintenance fluids through IV, serum electrolyte values should be monitored daily and therapy adjusted accordingly
- avoid iatrogenic hyper/hyponatremia, keep the possibility of SIADH in mind

# Gastroenterology

## Vomiting

**Vomiting:** forceful expulsion of stomach contents through the mouth
**Regurgitation:** the return of partially digested food from the stomach to the mouth

**Pyloric Stenosis 3 Ps**
**P**alpable mass
**P**eristalsis visible
**P**rojectile vomiting (2-4 wk after birth)

### History
- characteristic of emesis (e.g. projectile, bilious, bloody)
- pattern of emesis (e.g. association with feeds, cyclic, morning)
- associated symptoms (e.g. anorexia, diarrhea, etc.)
- red flags: bilious or bloody emesis, projectile vomit, abdominal distension and tenderness, high fever, signs of dehydration
- note that vomiting without diarrhea is often not gastroenteritis
  - post-tussive vomiting is also common with coughing fits in children

### Physical Findings
- vital signs to determine clinical status and hydration state

### Investigations
- CBC, electrolytes, BUN, Cr, amylase, lipase, glucose done routinely
- in sick child, add: ESR, venous blood gases, C&S (blood, stool), imaging

**Table 17. Common Differential Diagnosis, Associated Findings, and Diagnostic Approach Based on Age**

| Cause | Suggestive Findings | Diagnostic Approach |
|---|---|---|
| **NEONATES – NON-BILIOUS** | | |
| Tracheoesophageal Fistula | Vomiting, excessive secretions soon after birth (e.g. drooling, choking, respiratory distress), inability to feed, inability to advance NG tube | Inability to advance NG tube, CXR, upper GI series with water-soluble contrast |
| Pyloric stenosis | Projectile vomiting immediately after feeding, dehydrated, palpable "olive" in RUQ, decreased stools, hunger | U/S of pylorus, upper GI study (if U/S not diagnostic)<br>Electrolytes, ABG (hypokalemic, hypochloremic metabolic alkalosis) |
| GERD | Fussiness after feeds, spit ups, arching of back, poor weight gain | Empiric trial of acid suppression, pH monitoring study, upper GI study, endoscopy |
| Sepsis | Fever, lethargy, tachycardia, tachypnea, widening pulse pressure | CBC, cultures (blood, urine, CSF), CXR |
| Inborn error of metabolism | Poor feeding, FTT, jaundice, hepatosplenomegaly, cardiomyopathy, dysmorphia, developmental delay | Electrolytes, ABG (hyponatremic, hyperkalemic metabolic acidosis), lactate, ammonia, LFTs, BUN, Cr, serum glucose, bilirubin, PT/PTT, CBC |
| **NEONATES – BILIOUS** | | |
| Intestinal obstruction – malrotation with volvulus, meconium ileus | Bilious emesis, abdominal distension, pain, bloody stool, shock | AXR, upper GI series, contrast enema |
| Duodenal atresia/stenosis | Bilious emesis, abdominal distension, often seen in DS, jaundice, polyhydramnios during pregnancy. Hypokalemic, hypochloremic metabolic alkalosis | AXR, upper GI series ('double bubble' sign) |
| Hirschsprung's disease | Bilious emesis, abdominal distension, pain, failure to pass stool | AXR, upper GI series, contrast enema, rectal biopsy |
| Necrotizing enterocolitis | Premature neonate, bilious emesis, bloody stools, abdominal distension, intolerance of feeds | AXR, CBC |
| **CHILDREN AND ADOLESCENTS** | | |
| Acute viral gastroenteritis | Diarrhea, fever, sick contact, recent travel | CBC, stool culture |
| Appendicitis | Periumbilical discomfort that later localizes to RLQ, fever, anorexia | Abdominal U/S |
| Intussusception | Colicky progressive abdominal pain, drawing of legs up to chest, lethargy, bloody "red currant jelly" stool (Triad) | Abdominal U/S |
| Non-GI infection (e.g. meningitis) | Fever, localized findings depending on cause | Cultures (CSF, blood, urine), brain imaging, CXR |
| Increased ICP | Nocturnal wakening, progressive recurrent headache worse with Valsalva, nuchal rigidity | Brain CT without contrast<br>Therapeutic LP in idiopathic intracranial HTN |
| Toxic ingestion | Finding possibly varying by substance- toxidrome, often a history of ingestion | Qualitative and sometimes quantitative levels (urine, blood) |
| Pregnancy | Amenorrhea, morning sickness, bloating, breast tenderness | Urine β-hCG |
| Cyclic vomiting | At least 3 self-limited episodes of vomiting lasting 12 h, 7 d between episodes, no organic cause of vomiting | Diagnosis of exclusion |

### Management
- rehydration (see *Fluids and Electrolytes*, P33)
- treat underlying cause
- antiemetic drugs can be used in children >2 yr with severe vomiting: promethazine, prochlorperazine, metoclopramide, ondansetron

# Gastroesophageal Reflux

### Epidemiology
- extremely common in infancy (up to 50%) but rarely causes GERD

### Clinical Feature
- vomiting typically soon after feeding, non-bilious, rarely contains blood, small volume (<30 mL)
  - should suspect GERD, defined as when gastroesophageal reflux causes troublesome symptoms/complications
    - infant: poor weight gain, irritability, sleep disturbance, respiratory symptoms (coughing, choking, wheezing)
    - older child/adolescent: abdominal pain/heart burn, dysphagia, asthma, recurrent pneumonia/upper respiratory infections, recurrent otitis media, upper airway symptoms (chronic cough, hoarseness), dental erosions

### Investigations
- thriving baby requires no investigation
- GERD can be a clinical diagnosis but diagnostic investigations may include:
  - upper GI tract radiography – assesses anatomy and motility disorder
  - esophageal pH – quantify GER
  - upper endoscopy and esophageal biopsy – rule out other conditions that mimic GERD symptoms, assess GERD-related esophageal injury
  - warning signs of associated disorders requiring further investigations: bilious vomiting, GI tract bleeding, consistently forceful vomiting, fever, lethargy, hepatosplenomegaly, bulging fontanelle, micro/macrocephaly, seizures, abdominal tenderness/distension, suspected genetic, metabolic syndrome or chronic disease

### Management
- conservative (infant): thickened feeds, frequent and smaller feeds, elevation of head, changing formula to hydrolyzed protein or amino acid based formula
  - breastfeeding infants – mothers exclude milk and egg in diet
  - older children/adolescent – same as adult management
- medical
  - short-term parenteral feeding to enhance weight gain
  - ranitidine, PPI: decreases gastric acidity, decreases esophageal irritation
  - domperidone, metoclopramide: improves gastric emptying and GI motility; safety concerns and limited efficacy, should be reserved for children with gastroparesis contributing to GERD
- interventional: indicated for failure of medical therapy: - Nissen fundoplication – or insertion of gastrojejunal tube for post-pylorus feeds

### Complications
- esophagitis, strictures, Barrett's esophagus, FTT, aspiration, oral feeding aversion

# Tracheoesophageal Fistula

- see General Surgery, GS69

# Pyloric Stenosis

- see General Surgery, GS67

# Duodenal Atresia

- see General Surgery, GS68

# Malrotation of the Intestine

- see General Surgery, GS68

# Diarrhea

- definition of diarrhea varies with diet and age (stool normalcy difficult to define in children)
- infants → increase in stool frequency to twice as often per day; older children → 3+ loose or watery stools/d
- duration: acute: <2 wk; chronic: >2 wk

### Pathophysiology
- osmotic: due to non-absorbable solutes in GI tract (e.g. lactose intolerance)
- secretory: increased secretion of $Cl^-$ ions and water in intestinal lumen (e.g. bacterial toxin)
- malabsorption: less time for absorption due to increased motility or less villi to absorb (e.g. short bowel syndrome)



Diarrhea is defined as an increase in frequency and/or decreased consistency of stools compared to normal

Normal stool volume
Infants: 5-10 g/kg/d
Children: 200 g/d



**Diarrhea Red Flags**
Bloody stool, fever, petechiae or purpura, signs of severe dehydration, weight loss/FTT

### History
- frequency, duration, quality of diarrhea
- associated symptoms (e.g. fever, abdominal pain, hematochezia, etc.)
- recent antibiotic use or recent travel
- elements of diet

### Physical Findings
- vital signs to determine clinical status and hydration state

### Investigations
- acute diarrhea
  - stool for C&S, O&P, electron microscopy for viruses, *C. difficile* toxin, microscopy (leukocytes suggestive of invading pathogen), blood and urine cultures, blood work
- chronic diarrhea
  - serial heights, weights, growth percentiles
  - if child growing well and thriving, workup is limited (stool cultures as above, stool reducing substances)
  - red flags: poor growth, chronic rash, other serious infections, hospitalizations for dehydration (require full workup)
    - stool: consistency, pH, reducing substances, microscopy, occult blood, O&P, C&S, *C. difficile* toxin, 3 d fecal fat, α-1-antitrypsin clearance, fecal elastase
    - urinalysis, urine culture
    - CBC, differential, ESR/CRP, smear, electrolytes, total protein, albumin, carotene, $Ca^{2+}$, $PO_4^{3-}$, $Mg^{2+}$, Fe, ferritin, folate, fat-soluble vitamins, PTT, INR
    - sweat chloride, celiac screen, thyroid function tests, urine VMA and HVA, HIV test, lead levels
    - CXR, upper GI series and follow-through
    - specialized tests: endoscopy, small bowel biopsy

**Common Antibiotics that Can Lead to *C. difficile* Infection**
- Fluoroquinolones
- Clindamycin
- Penicillin (broad spectrum)
- Cephalosporincs (broad spectrum)

### Differential Diagnosis

**Table 18. Differential Diagnosis of Diarrhea**

| | Infectious | | | Non-infectious |
|---|---|---|---|---|
| **Acute** | **Viral**<br>Rotavirus<br>Norwalk<br>Enteric adenovirus | **Bacterial**<br>*Salmonella*<br>*Campylobacter*<br>*Shigella*<br>Pathogenic *E. coli*<br>*Yersinia*<br>*C. difficile* | **Parasitic**<br>*Giardia lamblia*<br>*Entamoeba histolytica* | Antibiotic-induced<br>Non-specific: associated with systemic infection<br>Hirschsprung's disease<br>Toxin ingestion<br>Primary disaccharidase deficiency |
| **Chronic** | **0 – 3 mo** | **3 mo – 3 yr** | **3 – 18 yr** | **Uncommon** |
| **No FTT** | GI infection | GI infection<br>Toddler's diarrhea | GI infection<br>Lactase deficiency<br>Irritable bowel syndrome | Drug-induced<br>Chronic constipation<br>UTI |
| **FTT** | Disaccharidase deficiency<br>Cow's milk protein intolerance<br>CF | Celiac disease | IBD<br>Endocrine (thyrotoxicosis, Addison's)<br>Neoplastic (pheochromocytoma, lymphoma) | Short bowel syndrome<br>Schwachman-Diamond syndrome |

## Gastroenteritis

### History
- non-specific: diarrhea, vomiting, fever, anorexia, headache, myalgias, abdominal cramps
- bacterial and parasitic agents more common in older children (2-4 yr)
- recent infectious contacts: symptoms usually begin 24-48 h after exposure

### Physical Exam
- febrile
- dehydrated: must assess extent (see *Approach to Infant/Child with Dehydration*, P33)

### Investigations
- not usually necessary in young children
- stool analysis: leukocytes/erythrocytes suggests bacterial or parasitic etiology; pH <6 and presence of reducing substances suggests viral etiology

### Complications
- viral gastroenteritis usually self-limiting (lasts 3-7 d in most cases)
- adverse effects related to hypovolemia, shock, tissue acidosis, and rapid onset and over-correction of electrolyte imbalances
- death in severe dehydration (rare in developed countries)

**Table 19. Gastroenteritis**

| | Viral Infection | Bacterial Infection |
|---|---|---|
| **Etiology** | Most common cause of gastroenteritis<br>Commonly: rotaviruses (most common), enteric adenovirus, norovirus (typically older children) | *Salmonella, Campylobacter, Shigella*, pathogenic *E. coli, Yersinia, C. difficile* |
| **Clinical Feature** | Associated with URTIs<br>Resolves in 3-7 d<br>Slight fever, malaise, vomiting, vague abdominal pain | Severe abdominal pain<br>High fever<br>Bloody diarrhea |
| **Risk Factors** | Daycare, young age, sick contacts, immunocompromised<br>Bacterial infection: travel, poorly cooked meat, poorly refrigerated foods, antibiotics | |
| **Management** | Prevention and treatment of dehydration most important (see *Dehydration*, P33)<br>Early refeeding advisable, with age-appropriate diet upon completion of rehydration<br>Ondansetron for suspected gastroenteritis with mild to moderate dehydration or failed ORT and significant vomiting<br>Antibiotic or antiparasitic therapy when indicated, antidiarrheal medications not indicated<br>Notify Public Health authorities if appropriate<br>Promote regular hand-washing and return to school 24 h after last diarrheal episode to prevent transmission<br>Rotavirus vaccine | |

# Toddler's Diarrhea

### Epidemiology
- most common cause of chronic diarrhea during infancy
- onset between 6-36 mo of age, ceases spontaneously between 2-4 yr

### Clinical Feature
- diagnosis of exclusion in thriving child
- 4-6 bowel movements per day
- diet history (e.g. excess juice intake overwhelms small bowel resulting in disaccharide malabsorption)
- stool may contain undigested food particles
- excoriated diaper rash

### Management
- reassurance that it is self-limiting
- 4Fs (adequate **F**ibre, normal **F**luid intake, 35-40% **F**at, discourage excess **F**ruit juice)

# Lactase Deficiency (Lactose Intolerance)

### Clinical Feature
- chronic, watery diarrhea and abdominal pain, bloating associated with dairy intake
- primary lactose intolerance: crampy abdominal pain with loose stool (older children, usually of East Asian and African descent)
- secondary lactose intolerance: older infant, persistent diarrhea (decreased lactase production post viral/bacterial infection, celiac disease, or IBD)

### Diagnosis
- trial of lactose-free diet
- watery stool, acid pH, positive reducing sugars
- positive breath hydrogen test if >6 yr

### Management
- lactose-free diet, soy formula
- lactase-containing tablets/capsules/drops (e.g. Lacteeze®, Lactaid®)

# Irritable Bowel Syndrome

- see Gastroenterology, G26

# Celiac Disease

- see Gastroenterology, G21
- in children: presents at any age, usually 6-24 mo with the introduction of gluten in the diet
- FTT with poor appetite, irritability, apathy, rickets, wasted muscles, flat buttocks, rarely distended abdomen
- GI symptoms: anorexia, N/V, edema, anemia, abdominal pain
- non-GI manifestations: iron-deficiency anemia, dermatitis herpetiformis, dental enamel hypoplasia, osteopenia/osteoporosis, short stature, delayed puberty, behavioural changes
- associated with other autoimmune disorders (e.g. Type 1 diabetes, MS, autoimmune hepatitis)



Celiac disease is associated with an increased prevalence of IgA deficiency. Since tTG is an IgA-detecting test, you must order an accompanying IgA level



A Celiac disease diet must avoid gluten present in "**BROW**" foods
**B**arley
**R**ye
**O**ats (controversial)
**W**heat

# Milk Allergy (MA) & Cow's Milk Protein Allergy

### Pathophysiology
- milk allergy (MA) is IgE mediated whereas cow's milk protein allergy (i.e. food protein induced proctocolitis of infancy [FPIPI]) is non-IgE mediated and more common

### Clinical Feature
- MA reactions occur within hours of exposure and are present on the skin (urticarial, pruritus), upper and lower resp tract symptoms (wheeze, cough)
- occurs between 2-8 mo of infancy, presents with:
  - proctocolitis: mild diarrhea, small amounts of bloody stools (common presentation in young infant)
  - enterocolitis: vomiting, diarrhea, anemia, hematochezia, constipation
  - enteropathy: chronic diarrhea, hypoalbuminemia
- up to 50% of children intolerant to cow's milk may be intolerant to soy protein as well

### Investigations
- food challenge (gold standard), skin prick test, serum measurement of allergen-specific IgE, patch testing

### Management
- MA: stop exposure
- FPIPI: stop, reintroduce milk at 6-8 mo, vast majority (>90%) will outgrow intolerance by 1 yr
- casein hydrolysate formula (dairy-free e.g. Nutramigen®, Pregestimil®) or mother may sequentially remove cow's milk protein, all bovine protein, soy protein, legumes (7 d washout), and continue breastfeeding (with adequate calcium and vitaminD intake)

# Inflammatory Bowel Disease

- see Gastroenterology, G22

# Cystic Fibrosis

- see *Respirology*, P82

# Constipation

- decreased stool frequency (<3 stools/wk) and/or stool fluidity (hard, pellet-like)

### FUNCTIONAL CONSTIPATION
- 99% of cases of constipation
- Rome III criteria
  - ≥2 of the following for at least 1 mo:
    - ≤2 defecations/wk
    - history of excessive stool retention
    - history of large-diameter stools
    - history of painful or hard bowel movements
  - in toilet trained children, the following additional criteria may be used:
    - at least one episode/wk of incontinence after the acquisition of toileting skills
    - history of large-diameter stools that may obstruct toilet

### Pathophysiology
- lack of fibre in diet or change in diet, poor fluid intake, behavioural
  - infants: often occurs when introducing cow's milk after breast milk due to high fat and solute content, lower water content
  - toddlers/older children: can occur during toilet training, or due to pain on defecation, leading to withholding of stool
  - two crucial time periods: toilet training and starting school

### Management
- education: explanation of mechanism of functional constipation for parents/older children
- clean out: PEG 3350 flakes (1-1.5 g/kg/d, max 100 g/d), picosalax, PEGlyte®
- maintenance: adequate fluid intake (if <6 mo, 150 mL/kg/d), adequate dietary fibre (fruit, vegetables, whole grains), stool softening (PEG 3350, mineral oil), appropriate toilet training technique (dedicated time for defecation: 3-10 min, 1-2 x/d)
- children should be treated for at least 6 mo, and should not be weaned from maintenance therapy until they are having regular bowel movements without difficulty
- regular follow-up with ongoing support and encouragement is essential

### Complications
- pain retention cycle: anal fissures + pain from withholding passing stool, chronic dilatation ± overflow incontinence

### HIRSCHSPRUNG'S DISEASE (Congenital Aganglionic Megacolon)
- see General Surgery, GS69

### OTHER ORGANIC DISORDERS CAUSING CONSTIPATION
- endocrine: hypothyroidism, DM, hypercalcemia
- neurologic: spinal cord abnormalities/trauma, NF
- anatomic: bowel obstruction, anus (imperforate, atresia, stenosis, anteriorly displaced)
- drugs: lead, chemotherapy, opioids
- others

# Abdominal Pain

### ACUTE ABDOMINAL PAIN

#### History
- description of pain (location, radiation, duration, constant vs. colicky, relation to meals)
- associated symptoms: N/V, diarrhea, fever

#### Physical Exam
- abdominal exam, rectal exam, rash

#### Investigations
- CBC, differential, urinalysis to rule out UTI

**Table 20. Differential Diagnosis of Acute Abdominal Pain**

| Gastrointestinal | Hepatobiliary Tract | Genitourinary | Hematologic | Metabolic | Drug and Toxins | Pulmonary | Miscellaneous |
|---|---|---|---|---|---|---|---|
| Gastroenteritis<br>Appendicitis<br>Mesenteric adenitis<br>Constipation<br>Ileus<br>Abdominal trauma<br>Intestinal obstruction (incarcerated hernia, intussusception, volvulus)<br>Peritonitis<br>Peptic ulcer<br>Meckel's diverticulum<br>IBS<br>Food poisoning<br>Lactose intolerance | Hepatitis<br>Cholecystitis<br>Cholelithiasis<br>Spleen – infarction, rupture<br>Pancreatitis | UTI<br>Urinary calculi<br>Dysmenorrhea<br>Mittelschmerz<br>PID<br>Threatened abortion<br>Ectopic pregnancy<br>Nephrolithiasis<br>Testicular torsion<br>Ovarian torsion<br>Endometriosis<br>Hematocolpos | Sickle cell crisis<br>Henoch-Schönlein purpura<br>Hemolytic uremic syndrome | Diabetic ketoacidosis<br>Hypoglycemia<br>porphyria | Erythromycin<br>salicylates<br>lead<br>poisoning<br>venoms | Pneumonia<br>Diaphragmatic pleurisy | Functional pain<br>Infantile colic<br>Pharyngitis<br>Angioneurotic edema<br>Mediterranean fever |

### APPENDICITIS
- see General Surgery, GS32
- most common cause of acute abdomen after 5 yr of age
- clinical features: low grade fever, abdominal pain, anorexia, N/V (after onset of pain), peritoneal signs (generalized peritonitis is a common presentation in infants/young children)
- treatment: surgical
- complications: perforation (common in young children), abscess

### INTUSSUSCEPTION
- telescoping of segment of bowel into distal segment causing ischemia and necrosis



**Intussusception – Classic Triad**
- Abdominal pain
- Palpable mass
- Red currant jelly stools

#### Epidemiology
- 90% idiopathic, children with CF or GJ tube at significantly increased risk; M:F = 3:1
- 50% between 3-12 mo, 75% before 2 yr of age

#### Pathophysiology
- usual site: ileocecal junction; jejunum in children with GJ tubes
- lead point of telescoping segment may be swollen Peyer's patches, Meckel's diverticulum, polyp, malignancy, HSP, structural abnormalities

#### Clinical Feature
- "classic triad" (<25% patients) - abdominal pain, palpable mass, red currant jelly stools
- often preceded by URTI
- sudden onset of recurrent, paroxysmal, severe periumbilical pain with pain-free intervals
- later vomiting (may be bilious) and rectal bleeding (late finding)
- shock and dehydration; lethargy may be only presenting symptom

#### Diagnosis
- U/S, air enema

### Management
- air enema can be therapeutic (reduces intussusception in 75% of cases), reduction under hydrostatic pressure, surgery rarely needed
- recurrence rate 10-15%, need to consider pathologic lead point

# Chronic Abdominal Pain

### Epidemiology
- prevalence: 10% of school children (peak at 8-10 yr), F>M

### Etiology
- organic (<10%)
  - gastrointestinal
    - constipation (cause vs. effect), infectious
    - IBD, esophagitis, peptic ulcer disease, lactose intolerance
    - anatomic anomalies, masses
    - pancreatic, hepatobiliary
    - celiac disease
  - genitourinary causes: recurrent UTI, nephrolithiasis, chronic PID, Mittelschmerz
  - neoplastic
- functional abdominal pain (90%): can be diagnosed when there are no alarming signs or symptoms, physical exam is normal, and stool sample tests are negative for occult blood; no further testing is required, unless high suspicion for organic cause
  - alarming symptoms include involuntary weight loss, deceleration of linear growth, GI blood loss, significant vomiting, chronic severe diarrhea, persistent upper or right lower quadrant pain, unexplained fever, family history of IBD
  - can be further subclassified into functional dyspepsia (pain in upper abdomen), irritable bowel syndrome (alternating bowel movements), abdominal migraine (paroxysmal abdominal pain, associated with anorexia, nausea, vomiting, pallor), functional abdominal pain syndrome

**Chronic Abdominal Pain**

**Rule of 3s**
3 episodes of severe pain
Child >3 yr old
Over 3 mo period

**Red Flags for Organic Etiology of Chronic Abdominal Pain**
- Age <5 yr old
- Fever
- Localizes pain away from midline
- Anemia
- Evidence of GI blood loss
- Rash
- Pain awakens child at night
- Travel history
- Prominent vomiting, diarrhea
- Weight loss or failure to gain weight
- Deceleration in linear growth
- Joint pain
- Family history of IBD
- Abnormal or unexplained physical exam findings

### Clinical Feature
- clustering episodes of vague, crampy periumbilical/epigastric pain, vivid pain description
- seldom awakens child from sleep, less common on weekends
- aggravated by exercise, alleviated by rest
- psychological factors related to onset and/or maintenance of pain, school avoidance
- psychiatric comorbidity: anxiety, somatoform, mood, learning disorders, sexual abuse, eating disorders, elimination disorders
- diagnosis of exclusion

### Investigations
- fecal occult blood and others based on clinical suspicion (CBC, ESR, urinalysis, etc.)

### Management
- continue to attend school
- manage any emotional or family problems, counselling, CBT
- trial of high fibre diet, trial of lactose-free diet
  - medication should be for symptom relief – acid reduction therapy for dyspepsia, antispasmodic agents, smooth muscle relaxants for pain, nonstimulating laxatives or antidiarrheals for altered bowel pattern
- possible role for amitriptyline
- reassurance

### Prognosis
- pain resolves in 30-50% of children within 2-6 wk of diagnosis
- 30-50% of children with functional abdominal pain have functional pain as adults (e.g. IBS)

# Abdominal Mass

**Table 21. Differential Diagnosis for Abdominal Mass**

| | Benign | Malignant |
|---|---|---|
| **Renal**<br>(note: 50% of abdominal masses in newborn are renal in origin) | Hydronephrosis<br>Polycystic kidney disease<br>Hamartoma | Nephroblastoma (Wilms' tumour)<br>Renal cell carcinoma |
| **Adrenal** | | Neuroblastoma |
| **Ovarian** | Ovarian cysts | Ovarian tumours |
| **Other** | Hepatomegaly/splenomegaly<br>Pyloric stenosis<br>Abdominal hernia<br>Teratoma<br>Fecal impaction | Lymphoma<br>Rhabdomyosarcoma<br>Retroperitoneal sarcoma |

**Table 22. Abdominal Mass**

| Abdominal Mass | Benign or Malignant | Clinical Feature | Management |
|---|---|---|---|
| Hydronephrosis | Benign | Usually asymptomatic<br>Urinary tract obstruction<br>Vesicoureteral reflux | Genetic counselling<br>Unilateral hydronephrosis >4 mm in second trimester, a follow-up US scan in third trimester is performed<br>Persistent hydronephrosis >10 mm require postnatal evaluation |
| Polycystic Kidney Disease | Benign | Progressive renal failure, hypertension, urinary tract infection, concentrating defects, hematuria, nephrolithiasis, flank pain | BP control with ACE inhibitors<br>Dietary sodium restrictions<br>Statins<br>Vasopressin receptor antagonists |
| Hamartoma | Benign | Asymptomatic abdominal swelling<br>Abdominal pain (30-40%)<br>Hematuria (12-25%)<br>Fever and hypertension (25%) | Surgery, chemotherapy, radiation |
| Wilm's Tumour | Malignant | Asymptomatic abdominal swelling<br>Abdominal pain (30-40%)<br>Hematuria (12-25%)<br>Fever and hypertension (25%) | Surgery, chemotherapy, radiation |
| Renal Cell Carcinoma | Malignant | Classic triad of flank pain, hematuria and palpable abdominal renal mass | For localized RCC, surgery is curative<br>For advanced RCC, immunotherapy and radiation |

# Upper Gastrointestinal Bleeding

- see Gastroenterology, G28

# Lower Gastrointestinal Bleeding

- see Gastroenterology, G30

## Etiology

- acute
  - infectious (bacterial, parasitic)
  - antibiotic-induced (*C. difficile*)
  - NEC in preterm infants
  - anatomic
  - malrotation/volvulus, intussusception
  - Meckel's diverticulitis
  - anal fissures, hemorrhoids
  - vascular/hematologic
  - HSP
  - HUS
  - coagulopathy
- chronic
  - anal fissures (most common)
  - colitis
  - IBD
  - allergic (milk protein)
  - structural
  - polyps (most are hamartomas)
  - neoplasms (rare)
  - coagulopathy

## Physical Exam

- hemodynamic status, evidence of FTT, fever
- anal and rectal exam: tags, fissures, anal fistulas, polyps, foreign body, blood per rectum
- stool appearance
- NG aspirate
- lower GI bleed may present as melena (if it involves the small bowel) or hematochezia

## Investigations

- stool cultures (C&S, *C. difficile* toxin)
- urinalysis and microscopy
- CBC, smear, differential, ESR, CRP, electrolytes, urea, Cr, INR, PTT, albumin, iron studies, amoeba titers
- radiologic investigations (including abdominal x-ray to rule out obstruction)
- Meckel's radionuclide scan

## Management

- acute stabilization: ABCs, volume and blood replacement, bowel rest (NPO, NG tube)
- once stable, endoscopy and/or surgery as indicated

# Genetics, Dysmorphisms, and Metabolism

- see Medical Genetics

# Hematology

## Approach to Anemia

### CLASSIFICATION

- mechanism: decreased production (inadequate reticulocyte response) vs. increased destruction or loss (adequate reticulocyte response)
  - in the context of anemia, a normal retic count is inappropriate

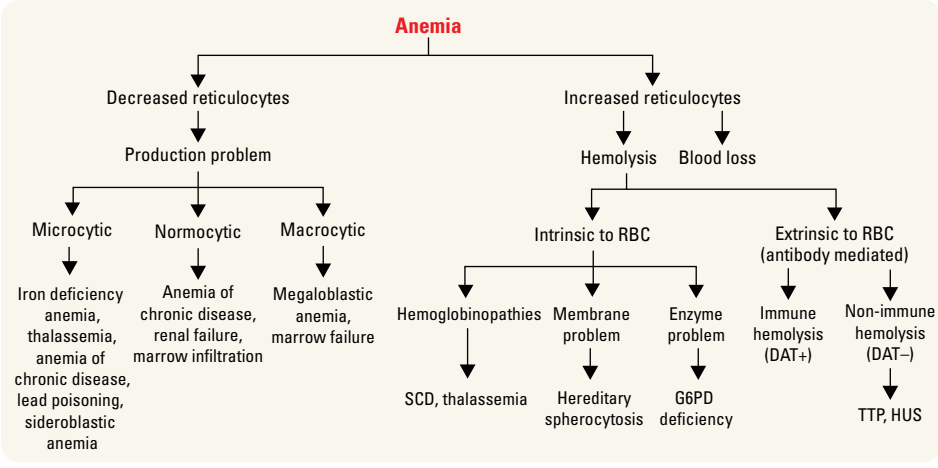



**Figure 11. Approach to anemia**

**Normal Hb Values by Age**

| Age | Hb Range (g/L) |
|---|---|
| Newborn | 137-201 |
| 2 wk | 130-200 |
| 3 mo | 95-145 |
| 6 mo-6 yr | 105-140 |
| 7-12 yr | 110-160 |
| Adult female | 120-160 |
| Adult male | 140-180 |

## Physiologic Anemia

- high Hb (>170 g/L) and reticulocyte count at birth is caused by a hypoxic environment in utero
- after birth, levels start to fall due to shorter fetal RBC lifespan, decreased RBC production (during first 6-8 wk of life, there is virtually no erythropoiesis due to new $O_2$ rich environment), and increasing blood volume secondary to growth
- lowest levels about 100 g/L at 8-12 wk age (earlier and more exaggerated in premature infants); levels rise spontaneously with activation of erythropoiesis
- usually no treatment required

MCV in childhood varies with age
Rule of thumb: lower normal limit of MCV = 70 + age (yr) until 80 fL (adult standard)

## Iron Deficiency Anemia

- most common cause of childhood anemia
- full term infants exhaust iron reserves by 6 mo of age
- premature infants have lower reserves, therefore exhausted by 2-3 mo of age
- common diagnosis between 6 mo-3 yr and 11-17 yr due to periods of rapid growth and increased iron requirements; adolescents also have poor diet and menstrual losses

Ferritin is an acute phase reactant, therefore, normal or high ferritin does not exclude iron deficiency anemia during an infection

### Etiology

- children at risk (premature, LBW, low SES, etc.)
- dietary risk factors: cow's milk in first year of life
- age >6 mo: <2 servings/d of iron-fortified cereal, red meat, or legumes
- age <12 mo: use of low-iron formula (<10 mg/L), primary diet of cow, goat, or soy milk
- age 1-5 yr: >16-20 oz/d of non-iron fortified milk
- blood loss
  - iatrogenic: repeated blood sampling (especially in hospitalized neonates)
  - allergic: cow's milk protein-induced colitis

Iron deficiency is rare in children <6 mo in the absence of blood loss or prematurity

### Clinical Feature

- usually asymptomatic until marked anemia
- symptoms may include: pallor, fatigue, pica (eating non-food materials), tachycardia, systolic murmur, angular cheilitis, koilonychia (spoon nails)

### Investigations

- CBC: low Hb, MCV, and MCH, reticulocyte count normal or high (absolute number low)
- Mentzer index (MCV/RBC) can help distinguish iron deficiency anemia from thalassemia
  - ratio <13 suggests thalassemia
  - ratio >13 suggests iron deficiency
- blood smear: hypochromic, microcytic RBCs, pencil shaped cells, poikylocytosis

- iron studies: low ferritin, other (low iron, high total iron binding capacity, high transferrin, low transferrin saturation)
- initial therapy: trial of iron

### Prevention
- breastfed term infants: begin iron supplementation (1 mg/kg/d) at 4-6 mo, continuing until able to eat ≥2 feeds/d of iron-rich foods
- non-breastfed (<50% of diet) term infants: give iron-fortified formula from birth
- premature infants: give iron supplements from 1 mo through to 1 yr of age
- no cow's milk until 9-12 mo, early introduction of red meat and iron-rich vegetables: total daily iron should be 11 mg (age 6-12 mo), 7 mg (age 1-3 yr)
- consider screening Hb levels in infants not receiving iron-fortified formula at 9-12 mo, and earlier if other risk factors

### Management
- encourage diverse, balanced diet, limit homogenized milk to 16-20 oz/d
- oral iron therapy: 4-6 mg/kg/d elemental iron, divided bid to tid, for 3- 6 mo to replenish iron stores
  - increased reticulocyte count in 2-3 d (peaks day 5-7)
  - increased hemoglobin in 4-30 d
  - repletion of iron stores in 1-3 mo
  - repeat hemoglobin levels after 1 mo of treatment
- poor response to oral iron therapy: non-adherance, medication intolerance, ongoing blood loss, IBD, celiac disease, incorrect diagnosis

### Complications
- can cause irreversible effects on development if untreated (behavioural and intellectual deficiencies)
- angular cheilitis, glossitis, koilonychia (spoon nails)

## Vitamin K Deficiency

### Etiology
- hemorrhagic disease of the newborn (HDNB) due to relative deficiencies of vitamin K-dependent coagulation factors
  - generalized bleeding; GI/intracranial hemorrhage
  - early-onset (in first 24 hours), classic (day 2 to 2 weeks), and late-onset (2 weeks up to 3-6 mo)
- IM injection at birth, can also be given orally (3 doses: at birth, 2-4 wk, 6-8 wk) but infants at higher risk of HDNB
- reason for administration at birth:
  - insufficient prenatal storage of vitamin K and human milk contains small amounts of vitamin K
  - risk factors for non-classic presentation: maternal medication (i.e. antiepileptic drugs), chronic malabsorption, no prophylaxis

## Anemia of Chronic Disease

- see Hematology, H16

## Sickle Cell Disease

- see Hematology, H20

## Thalassemia

- see Hematology, H19

## Hereditary Spherocytosis

- see Hematology, H22

## Glucose-6-Phosphate Dehydrogenase Deficiency

- see Hematology, H23



G6PD deficiency protects against parasitism of RBCs (i.e. malaria)

## Bleeding Disorders

- see Hematology, H25

**Table 23. Evaluation of Abnormal Bruising/Bleeding**

| | PFA | PT | PTT | VIII:C | vWF | Platelets | Fibrinogen |
|---|---|---|---|---|---|---|---|
| **Hemophilia A** | N | N | ↑ | ↓ | N | N | N |
| **Hemophilia B** | N | N | ↑ | N | N | N | N |
| **von Willebrand Disease** | ↑ | N | N or ↑ | ↓ | N or ↓ | N | N |
| **DIC** | N or ↑ | ↑ | ↑ | ↓ | N | ↓ | ↓ |
| **Vitamin K Deficiency** | N | ↑ | ↑ | N | N | N | N |
| **Thrombocytopenia** | ↑ | N | N | N | N | ↓ | N |

DIC = disseminated intravascular coagulation; PFA = platelet function assay; VIII:C = Factor VIII coagulant activity; vWF = von Willebrand Factor

Extensive bruising in the absence of lab abnormalities: consider child maltreatment

# Immune Thrombocytopenic Purpura

## Epidemiology
- most common cause of thrombocytopenia in childhood
- peak age: 2-6 yr, M=F
- incidence 5:100,000 children per year

## Etiology
- caused by autoantibodies that bind to platelet membranes → Fc-receptor mediated splenic uptake → destruction of platelets

## Clinical Feature
- 50% present 1-3 wk after viral illness (e.g. URTI, chicken pox)
- sudden onset of petechiae, purpura, epistaxis in an otherwise well child
- clinically significant bleed in only 3% (severe bleed more likely with platelet count <10) with <0.5% risk of intracranial bleed
- no lymphadenopathy, no hepatosplenomegaly
- labs: thrombocytopenia with normal RBC, WBC
- bone marrow aspirate only if atypical presentation (≥1 cell line abnormal, hepatosplenomegaly)
- differential diagnosis: leukemia, drug-induced thrombocytopenia, HIV, infection (viral), autoimmune (SLE, ALPS)

## Management
- observation vs. pharmacologic intervention highly debated; spontaneous recovery in >70% of cases within 3 mo
- involve family in management; shared decision-making
- no or mild bleeding – strongly consider observation
- moderate bleeding (i.e. severe skin manifestations with some mucosal lesions and some troublesome epistaxis or menorrhagia) – IVIG or steroids; if Rh-positive can use anti-D but not first line due to serious adverse effects
- severe (i.e. prolonged epistaxis, GI bleeding or intracranial hemorrhage) - immediate treatment with IV steroids and IVIG; may use transexamic acid as adjunct therapy
- treatment with IVIg or prednisone if mucosal or internal bleeding, platelets <10, or at risk of significant bleeding (surgery, dental procedure, concomitant vasculitis or coagulopathy)
- life-threatening bleed: additional platelet transfusion ± emergency splenectomy
- persistent (>3-12 mo) or chronic (>12 mo): re-evaluate; treat if symptoms persist
- supportive: avoid contact sports and ASA/NSAIDs

**The American Society of Hematology 2011 Evidence-Based Practice Guideline for Immune Thrombocytopenia**
Blood 2011;117(16):4190-207

**Recommendations**
- Bone marrow examination is unnecessary in children and adolescents with the typical features of ITP.
- Bone marrow examination is not necessary in children who fail IVIg therapy (grade 1B).
- Children with no bleeding or mild bleeding (defined as skin manifestations only, such as bruising and petechiae) may be managed with observation alone regardless of platelet count.
- For pediatric patients requiring treatment, a single dose of IVIg (0.8-1 g/kg) or a short course of corticosteroids may be used as first-line treatment.
- IVIg can be used if a more rapid increase in the platelet count is desired.
- Anti-D therapy is not advised in children with a hemoglobin concentration that is decreased due to bleeding, or with evidence of autoimmune hemolysis.

**Suggestions**
- Bone marrow examination is also not necessary in similar patients prior to initiation of treatment with corticosteroids or before splenectomy.
- Testing for antinuclear antibodies is not necessary in the evaluation of children and adolescents with suspected ITP.
- A single dose of anti-D can be used as first-line treatment in Rh-positive, nonsplenectomized children requiring treatment.

# Hemophilia

- see Hematology, H31

# von Willebrand's Disease

- see Hematology, H30

# Oncology

- cancer is the second most common cause of death after injuries in children >1 yr of age
- cause is rarely known, but increased risk for children with: chromosomal syndromes (e.g. Trisomy 21), cancer predisposition syndromes (e.g. Li-Fraumeni syndrome), prior malignancies, neurocutaneous syndromes, immunodeficiency syndromes, family history, exposure to radiation, chemicals, biologic agents
- leukemias are the most common type of pediatric malignancy (30%) followed by brain tumours (25%), and lymphomas (15%)
- some malignancies are more prevalent in certain age groups
  - newborns: neuroblastoma, Wilms' tumour, retinoblastoma
  - infancy and childhood: leukemia, neuroblastoma, CNS tumours, Wilms' tumour, retinoblastoma
  - adolescence: lymphoma, gonadal tumours, germ cell tumours, bone tumours
- unique treatment considerations in pediatrics because radiation, chemotherapy, and surgery can impact growth and development, endocrine function, and fertility
- good prognosis: treatments have led to remarkable improvements in overall survival and cure rates for many pediatric cancers (>80%)

# Lymphadenopathy

### Clinical Features

- features of malignant lymphadenopathy: firm, discrete, non-tender, enlarging, immobile, abnormal imaging findings or bloodwork, constitutional symptoms, worrisome location (i.e. supraclavicular or generalized)
- fluctuance, warmth, or tenderness are more suggestive of benign nodes (infection)

### Differential Diagnosis

- infection
  - viral: URTI, EBV, CMV, adenovirus, HIV
  - bacterial: *S. aureus*, GAS, anaerobes, *Mycobacterium* (e.g. TB), cat scratch disease (*Bartonella*)
  - other: fungal, protozoan, Rickettsia
- autoimmune: rheumatoid arthritis, SLE, serum sickness
- malignancy: lymphoma, leukemia, metastatic solid tumours
- storage diseases: Niemann-Pick, Gaucher's
- other: sarcoidosis, Kawasaki disease, histiocytoses

### Investigations



Most common cause of acute bilateral cervical LAD is viral illness

- generalized lymphadenopathy
  - CBC and differential, blood culture
  - inflammatory markers (ESR, CRP)
  - serology: EBV, CMV and others as indicated (e.g. HIV, fungal, toxoplasmosis)
  - uric acid, LDH, electrolytes
  - CXR
  - TST
  - if indicated other blood work i.e. inflammatory panel (ANA, RF, dsDNA)
  - biopsy: if increasing in size; or >2 cm and unclear diagnosis or no response to treatment. Do early biopsy if supraclavicular or very large single or group of nodes (>3-4 cm)
- regional lymphadenopathy
  - period of observation if asymptomatic
  - trial of oral antibiotics
  - ultrasound
  - biopsy (especially if persistent >6 wk and/or constitutional symptoms)

# Leukemia

- see Hematology, H38

### Epidemiology

- mean age of diagnosis 2-5 yr but can occur at any age
- heterogeneous group of diseases
  - ALL (80%)
  - AML (15%)
  - CML (<5%)
- children with DS are 15x more likely to develop leukemia

### Clinical Feature

- infiltration of leukemic cells into bone marrow results in bone pain and bone marrow failure (anemia, neutropenia, thrombocytopenia)
- infiltration into tissues results in lymphadenopathy, hepatosplenomegaly, CNS manifestations, testicular disease

- fever, fatigue, weight loss, bruising, and easy bleeding
- investigations: CBC and differential, peripheral blood smear, uric acid, LDH, extended electrolytes, renal function and blood culture
- specialized tests: BM ± lymph node biopsy, flow cytometry, cytogenetics, molecular studies
- hyperleukocytosis (total WBC >100 x $10^9$/L) is a medical emergency
  - presents clinically with respiratory or neurological distress caused by hyperviscosity of blood and leukostasis
  - risk of ICH, pulmonary leukostasis syndrome, tumour lysis syndrome
  - management: fluids, allopurinol/rasburicase, fresh frozen plasma/platelets to correct thrombocytopenia, induction chemotherapy, avoid transfusing RBCs unless symptomatic (and then use very small volumes)

### Management
- combination chemotherapy using non-cross resistant chemotherapy agents, allogeneic stem cell transplantation for high-grade or recurrent disease
- supportive care and management of treatment complications
  - febrile neutropenia: see Infectious Diseases, ID42
  - tumour lysis syndrome: see Hematology, H52

### Prognosis
- 80-90% 5 yr event-free survival for ALL, 50-60% 5-yr survival for AML
- patients are stratified into standard risk and high risk based on WBC and age; other prognostic factors include presence of CNS/testicular disease, immunophenotype, cytogenetics, and initial response to therapy (most important prognostic variable)

## Lymphoma

- see Hematology, H45

### Epidemiology
- Hodgkin lymphoma: incidence is bimodal, peaks at ages 15-34 and >50 yr old
- non-Hodgkin lymphoma: incidence peaks at 7-11 yr

### Clinical Feature
- Hodgkin lymphoma
  - most common presentation is persistent, painless, firm, cervical or supraclavicular lymphadenopathy
  - can present as persistent cough or dyspnea (secondary to mediastinal mass) or less commonly as splenomegaly, axillary, or inguinal lymphadenopathy
  - constitutional symptoms in 30% of children
  - lymph nodes become sequentially involved as disease spreads
- non-Hodgkin lymphoma
  - generally categorized into lymphoblastic, diffuse large B cell, Burkitt's lymphoma, and anaplastic large cell
  - rapidly growing tumour with distant metastases (unlike adult non-Hodgkin lymphoma)
  - signs and symptoms related to disease site: most commonly abdomen, chest (mediastinal mass), head and neck region
- investigations: CBC and differential, peripheral blood smear, extended electrolytes, uric acid, LDH, renal function, liver enzymes and function, ESR, ferritin, and blood culture if concerns for infection. CXR and CT of chest/abdomen/pelvis. Specialized tests: BM aspirate and biopsy ± LN biopsy, lumbar puncture, nuclear medicine scans



Back pain in children must always be investigated!
Unlike adults, back pain in children often points to a pathological process

### Management
- Hodgkin lymphoma
  - combination chemotherapy and radiation
  - increasing role for use of PET scanning to assess early disease response and plan therapy
- non-Hodgkin lymphoma
  - combination chemotherapy
  - no added benefit of radiation in pediatric protocols



Constitutional symptoms = fever, chills, night sweats, unexplained weight loss

### Prognosis
- Hodgkin lymphoma: >90% 5 yr survival
- non-Hodgkin lymphoma: 75-90% 5 yr survival

## Brain Tumours

- see Neurosurgery, NS38

# Wilms' Tumour (Nephroblastoma)

### Epidemiology
- usually diagnosed between 2-5 yr; M=F
- most common primary renal neoplasm of childhood
- 5-10% of cases both kidneys are affected (simultaneously or in sequence)

### Differential Diagnosis
- hydronephrosis, polycystic kidney disease, renal cell carcinoma, neuroblastoma

### Clinical Feature
- 80% present with asymptomatic, unilateral abdominal mass
- may also present with HTN, gross hematuria, abdominal pain, vomiting
- may have pulmonary metastases at time of diagnosis (respiratory symptoms)

### Associated Congenital Abnormalities
- **WAGR** syndrome (**W**ilms' tumour, **A**niridia, **G**enital anomalies, mental **R**etardation) with 11p13 deletion
- Beckwith-Wiedemann syndrome:
  - characterized by enlargement of body organs (especially tongue), hemihypertrophy, renal medullary cysts, and adrenal cytomegaly
  - also at increased risk for developing hepatoblastoma, and less commonly adrenocortical tumours, neuroblastomas, and rhabdomyosarcomas
- Denys-Drash syndrome: characterized by gonadal dysgenesis and nephropathy leading to renal failure

### Management
- staging ± nephrectomy
- chemotherapy, radiation for higher stages

### Prognosis
- 90% long-term survival

# Neuroblastoma

### Epidemiology
- most common cancer occurring in first year of life
- neural crest cell tumour arising from sympathetic tissues (neuroblasts)

### Clinical Feature
- can originate from any site in sympathetic nervous system, presenting as mass in neck, chest, or abdomen (most common site is adrenal gland)
- signs and symptoms of disease vary with location of tumour
  - thoracic: dyspnea, Horner's syndrome
  - abdomen: palpable mass
  - spinal cord compression
- metastases are common at presentation (>50% present with advanced stage disease):
  - usually to bone or bone marrow (presents as bone pain, limp)
  - can also present with periorbital ecchymoses, abdominal pain, emesis, fever, weight loss, anorexia, hepatomegaly, "blueberry muffin" skin nodules
- paraneoplastic: HTN, palpitations, sweating (from excessive catecholamines), diarrhea, FTT (from vasoactive intestinal peptide secretion), opsomyoclonus

### Management
- depends on prognostic factors and may include combination of: surgery, radiation, chemotherapy, autologous stem cell transplantation, immunotherapy

### Prognosis
- prognosis is often poor due to late detection
- good prognostic factors
  - "age and stage" are important determinants of better outcome: <18 mo, stage I, II, IV-S disease ("S" designates a "Special" classification only pertaining to infants)
  - primary site: posterior mediastinum and neck
  - low serum ferritin
  - more differentiated histology
  - tumour cell markers: aneuploidy, absent MYCN oncogene amplification

# Bone Tumours

- see Orthopedic Surgery, OR46

# Cancer Predisposition Syndromes

- suspected in cases of multiple primary neoplasms, especially early onset for cancer type and/or family history consistent with known cancer predisposition syndrome (critical to obtain family history and refer if syndrome suspected)
- cancer predisposition syndromes with pediatric onset include Li-Fraumeni syndrome (soft tissue sarcomas, osteosarcoma, CNS tumours and adrenal cortical carcinoma), hereditary retinoblastoma, and Fanconi anemia (leukemias)

# Infectious Diseases

## Fever

### Definition

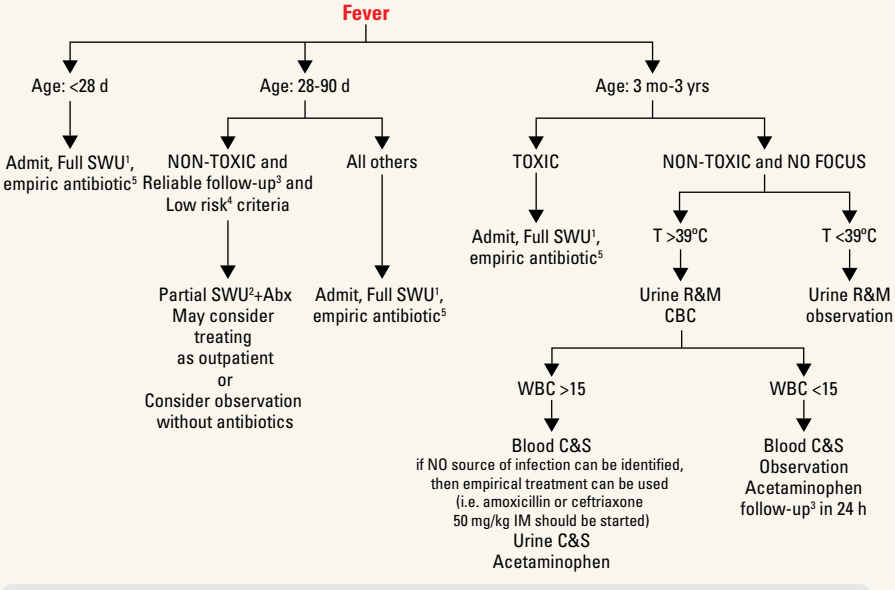
- fever: a practical definition is >38°C/100.4°F oral or rectal
- fever without a source/focus: acute febrile illness (typically <10 d duration) with no cause of fever even after careful history and physical
- fever of unknown origin: daily or intermittent fevers for at least 2 consecutive wk of uncertain cause after careful history and physical, and initial laboratory assessment

### Etiology

- infectious: anatomic approach (CNS, ears, upper and lower respiratory tract, GI, GU, skin, soft tissue, bones and joints, etc.)
- inflammatory: mainly autoimmune (Kawasaki disease, JIA, IBD, SLE, etc.)
- malignancy: childhood cancers (leukemia, lymphoma, neuroblastoma, etc.)
- miscellaneous: dehydration, drugs and toxins, post-immunization, familial dysautonomia, factitious disorder, etc.

### Diagnosis

- history: duration, height and pattern of fever, associated symptoms, exposures, constitutional symptoms, recent antipyretic use, ethnic or genetic background, daycare, sick contacts, travel, tick bites, age of child
- physical exam: toxic vs. non-toxic, vitals, growth, complete exams of the skin, HEENT, chest, abdomen, lymph nodes, genitalia
- investigations: guided by history, physical exam, and clinical suspicion




**NOTES**
1. SWU = Septic Workup
2. Partial Septic Workup – blood C&S, CBC and differential, urine R&M, C&S, LP, CXR if respiratory symptoms, stool C&S if GI symptoms
3. Follow-up is crucial – if adequate follow-up is not assured, a more aggressive diagnostic and therapeutic approach may be indicated
4. Low-risk (Rochester) criteria
5. Considerable practice variation exists in terms of empiric antibiotic treatment
6. Important principles – the younger the child, the greater the difficulty to clinically assess the degree of illness

**Figure 12. Approach to the febrile child**

**Rochester Criteria – Developed to Identify Infants ≤60 d of Age with Fever at Low Risk of Serious Bacterial Infection**

| | |
|---|---|
| Clinically | Well |
| WBC Count | 5-15 x $10^9$/L |
| Bands | <1.5 x $10^9$/L |
| Urinalysis | <10 WBC/HPF |
| Stool (if diarrhea) | <5 WBC/HPF |
| Past Health | Born >37 wk<br>Home with/before mom<br>No hospitalizations<br>No prior antibiotic use<br>No prior treatment for unexplained hyperbilirubinemia<br>No chronic disease |

### Evaluation of Neonates and Infants with Fever
- several protocols exist that attempt to identify neonates and young infants at low risk of serious bacterial infection (e.g. Rochester Criteria)
  - such protocols are not as sensitive in the 1-28 d age group; therefore, febrile neonates should be considered high risk regardless of clinical features and laboratory findings

### Management
- admit to hospital if appropriate
- treat the source if known
- replace fluid losses (e.g. from vomiting, diarrhea, etc.); maintenance fluid needs are higher in febrile child
- reassure parents that most fevers are benign and self-limited
- antipyretics (acetaminophen and/or ibuprofen) may be given if child is uncomfortable

## Acute Otitis Media

All of:
1. presence of middle ear effusion
2. presence of middle ear inflammation
3. acute onset of symptoms of middle ear effusion and inflammation

### Epidemiology
- 60-70% of children have at least 1 episode of AOM before 3 yr of age
- 18 mo-6 yr most common age group
  - 22% of children in this age range will develop AOM in the first wk of a viral URI
- one third of children have had ≥3 episodes by age 3; peak incidence January to April

### Etiology
- bacterial – *S. pneumoniae* (decreasing since the introduction of PCV7 and PCV13), *H. influenza, M. catarrhalis*, GAS
- less common - anaerobes (newborns) , Gram-negative enterics (infants)
- viral – more likely to spontaneously resolve

### Risk Factors
- Eustachian tube related:
  - dysfunction/obstruction (URTI, allergic rhinitis, chronic rhinosinusitis, adenoid hypertrophy, barotrauma)
  - inadequate tensor palatine function (cleft palate)
  - genetic syndromes (DS, Crouzon, Apert)
  - cilia disruption (Kartagenger's syndrome, CF)
- genetic predisposition (family history, ethnicity – First Nations and Inuit, low levels of secretory IgA or persistent biofilm in middle ear)
- behavioural and environmental exposures (not breastfed or shorter duration of breastfeeding, prolonged bottle feeding, bottle feeding laying down, pacifier use, second-hand smoke exposure, crowded living conditions/daycare, sick contacts)
- immunosuppression/deficiency (chemotherapy, steroids, DM, hypogammaglobulinemia, CF)

### Pathogenesis
- obstruction of Eustachian tube → air absorbed in middle ear → negative pressure (an irritant to middle ear mucosa) → edema of mucosa with exudate/effusion → infection of exudate from nasopharyngeal secretions

### Clinical Features
- acute onset of symptoms
- triad of otalgia, fever (especially in younger children), and conductive hearing loss – not all symptoms such as fever or hearing loss may be present
- rarely tinnitus, vertigo, and/or facial nerve paralysis
- otorrhea if tympanic membrane perforated
- infants/toddlers: ear-tugging (this alone is not a good indicator of pathology), hearing loss, balance disturbances (rare), irritable, poor sleeping, vomiting and diarrhea, anorexia
- otoscopy of TM: hyperemia, bulging, pus may be seen behind TM, loss of landmarks (e.g. handle and long process of malleus not visible), discolouration (hemmorhagic, grey, red, yellow)

### Diagnosis
- requires middle ear effusion and signs of inflammation (most important is a bulging TM)

### Management
- symptomatic therapy: antipyretics/analgesics (e.g. acetaminophen or ibuprophen)
- watchful waiting if criteria met (see table 10)
- antibiotic therapy if <6 mo or moderate-severe illness:
  - 1st line: high dose amoxicillin 75-90 mg/kg/d dosed BID (if penicillin allergic: macrolides, TMP-SMX)
  - 2nd line: amoxicillin-clavulanic acid, cephalosporins: cefuroxime axetil, ceftriaxone, cefaclor, cefixime
    - used when AOM unresponsive and clinical signs/symptoms persist beyond 48 h of antibiotic treatment, or for treatment of otitis-conjunctivitis syndrome

**Clinical Assessment of AOM in Pediatrics**
JAMA 2010;304:2161-2169
**Purpose**: To summarize the evidence on AOM diagnosis, treatment and the association of the heptavalent pneumococcal conjugate vaccine (PCV7) use with AOM microbiology.
**Methods**: Systematic review of diagnostic studies with a criterion standard, observational studies, and RCTs comparing AOM microbiology with and without PCV7, and RCTs assessing antibiotic treatment.
**Results**: 135 studies were included. Otoscopic findings of tympanic membrane bulging (positive likelihood ratio (PLR 51, 95% CI 36-73) and redness (PLR 8.4, 7-11) were associated with accurate diagnosis. Prevalence of S. pneumoniae decreased while that of H. influenza increased pre vs. post-PCV7. Clinical success was higher with immediate ampicillin or amoxicillin versus placebo (73% vs. 60%; pooled rate difference 12%, 95% CI 5-18%; NNT 9, 95% CI 6-20). The risk of rash or diarrhea was increased by 3 to 5%. Some evidence suggested greater success with immediate versus delayed antibiotics. No significant differences were seen in terms of comparative effectiveness of antibiotics.
**Conclusion**: Otoscoipc findings are critical to accurate AOM diagnosis. Antibiotics are somewhat more effective than no treatment despite a higher incidence of adverse effects, and generally are comparatively equal in effectiveness.

**The Diagnosis and Management of Acute Otitis Media**
Pediatrics 2013;131:e964-e999
**Recommendations**
- Management of AOM should include an assessment of pain; if pain is present, the clinician should recommend treatment to reduce pain.
- Prescribe antibiotic therapy for AOM (bilateral or unilateral) in children 6 mo and older with severe signs or symptoms (i.e. moderate or severe otalgia or otalgia for at least 48 h or temperature 39°C [102.2°F] or higher).
- For bilateral or unilateral AOM in children 6 mo through 23 mo of age without severe signs or symptoms (i.e. mild otalgia for less than 48 h and temperature less than 39°C [102.2°F]) either prescribe antibiotic therapy or offer observation with close follow-up based on joint decision-making with the parent(s)/caregiver(s). With observation ensure follow-up and begin antibiotic therapy if the child worsens or fails to improve within 48-72 h of onset of symptoms.
- Do NOT prescribe prophylactic antibiotics to reduce the frequency of episodes of AOM in children with recurrent AOM.
- Recommend annual influenza vaccine and pneumococcal conjugate vaccine to all children according to vaccination schedule.

**Option**
- Offer tympanostomy tubes for recurrent AOM (3 episodes in 6 mo or 4 episodes in 1 yr with 1 episode in the preceding 6 mo).

- signs of a perforated TM should always be treated with antimicrobial therapy (most commonly topical Ciprodex) and examined for complications
- prevention: parent education about risk factors, pneumococcal and influenza vaccines, surgery (e.g. tympanostomy tubes)
  - choice of surgical therapy for recurrent AOM depends on whether local factors (Eustachian tube dysfunction) are responsible (use ventilation tubes), or regional disease factors (tonsillitis, adenoid hypertrophy, sinusitis) are responsible

### Complications
- extracranial: hearing loss and speech delay (secondary to persistent middle ear effusion), TM perforation, extension of suppurative process to adjacent structures (mastoiditis, petrositis, labyrinthitis), cholesteatoma, facial nerve palsy, middle ear atelectasis, ossicular necrosis, vestibular dysfunction
- intracranial: meningitis, epidural and brain abscess, subdural empyema, lateral and cavernous sinus thrombosis, carotid artery thrombosis

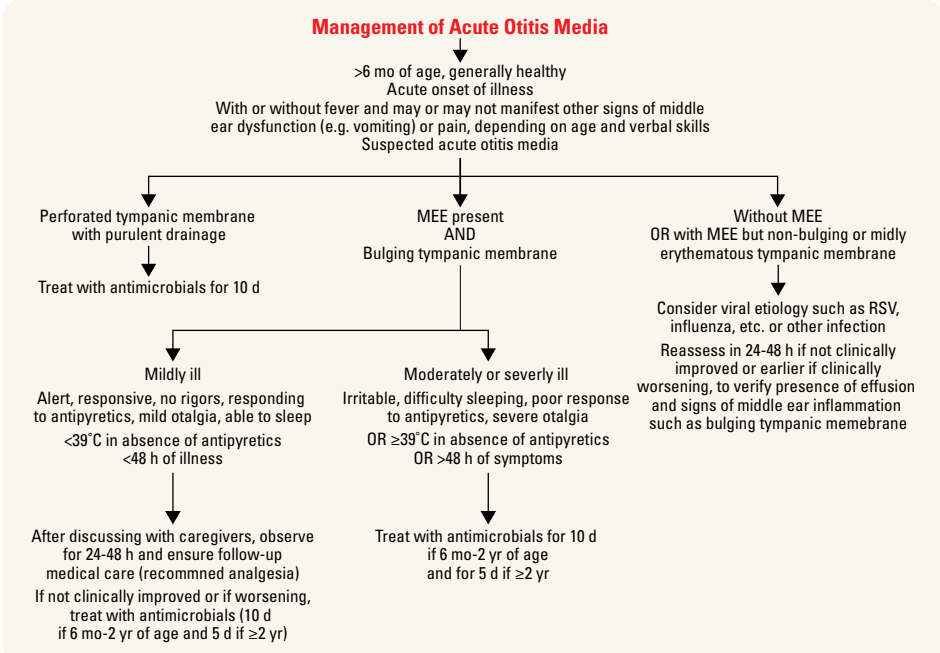



**Figure 13. Management of acute otitis media**
Flow diagram for the management of children with suspected and confirmed acute otitis media – from CPS statement Feb 2016

# Otitis Media with Effusion

### Definition
- presence of fluid in the middle ear without signs or symptoms of ear infection

### Epidemiology
- most common cause of pediatric hearing loss
- not exclusively a pediatric disease
- follows AOM frequently in children
- middle ear effusions have been shown to persist following an episode of AOM for 1 mo in 40% of children, 2 mo in 20%, and >3 mo in 10%

### Risk Factors
- same as AOM

### Clinical Features
- conductive hearing loss ± tinnitus
- fullness – blocked ear
- ± pain, low grade fever
- otoscopy of TM
  - discolouration – amber or dull grey
  - meniscus fluid level behind TM
  - air bubbles
  - retraction pockets/TM atelectasis
  - flat tympanogram
  - most reliable finding with pneumatic otoscopy is immobility

### Treatment
- expectant: 90% resolve by 3 mo
- document hearing loss with audiogram (see Otolaryngology Figure 16B and Figure 17B, OT10)
- no statistical proof that antihistamines, decongestants, antibiotics clear disease faster
- surgery: myringotomy ± ventilation tubes ± adenoidectomy (if enlarged or on insertion of second set of tubes after first set falls out)
- ventilation tubes to equalize pressure and drain ear

### Complications
- hearing loss, speech delay, learning problems in young children
- chronic mastoiditis
- ossicular erosion
- cholesteatoma especially when retraction pockets involve pars flaccida
- retraction of tympanic membrane, atelectasis, ossicular fixation

## Gastroenteritis

- see *Gastroenterology*, P37

## HIV Infection

- see Infectious Diseases, ID25

## Infectious Pediatric Exanthems

**Table 24. Common Infectious Pediatric Exanthems**

| Disease | Pathogen(s) | Incubation Period | Communicability | Mode of Transmission | Rash | Associated Features | Management | Outcomes and Complications |
|---|---|---|---|---|---|---|---|---|
| **Erythema Infectiosum** (i.e. Fifth Disease/ Slapped Cheek) | Parvovirus B19 | 4-14 d | Low risk of transmission once symptomatic | Respiratory secretions or infected blood | Appearance: uniform, erythematous, maculopapular 'lacy' rash<br>Timing: 10-17 d after symptoms (immune response)<br>Distribution: bilateral cheeks ('slapped cheeks') with circumoral sparing; may affect trunk and extremities | Initial 7-10 d of flu-like illness and fever<br>Rash may be warm, non-tender, and pruritic<br>Less common presentations include 'gloves and socks syndrome' or STAR complex (sore throat, arthritis, rash) | Supportive | Rash fades over days to week, but may reappear months later with sunlight, exercise<br>Aplastic crisis |
| **Gianotti-Crosti Syndrome** (i.e. Papular Acrodermatitis) | EBV and Hep B (majority) | Variable | None | — | Appearance: asymptomatic symmetric papules<br>Distribution: face, cheeks, extensor surfaces of the extremities, spares trunk | Viral prodrome<br>May have lymphadenopathy and/ or hepatosplenomegaly | Supportive<br>Pain control | Resolves in 3-12 wk |
| **Hand, Foot, and Mouth Disease** | Coxsackie group A | 3-5 d | Likely 1-7 d after symptoms but may be up to months | Direct and indirect contact with infected bodily fluids, fecal-oral | Appearance: vesicles and pustules on an erythematous base<br>Distribution: acral, but may exentend up the extremity | Enanthem: vesicles in the POSTERIOR oral cavity (pharynx, tongue) | Supportive | Mainly dehydration |
| **Herpes Simplex** | HSV 1, 2 | 1-26 d | | Direct contact, often through saliva for HSV-1 and sexual contact for HSV-2 | Grouped vesicles on an erythematous base | Enanthem: vesicles/erosions in the ANTERIOR oral cavity (buccal mucosa, tongue)<br>May present with herpetic whitlow (autoinoculation) | Mainly supportive<br>Consider oral or topical antivirals | Local: secondary skin infections, keratitis, gingivostomatitis<br>CNS: encephalitis<br>Disseminated hepatitis, DIC<br>Eczema herpeticum |
| **Kawasaki Disease** | See P88 | | | | | | | |
| **Measles** | Morbillivirus | 8-13 d | 4 d before and after rash | Airborne | Appearance: erythematous maculopapular<br>Timing: 3 d after start of symptoms<br>Distribution: starts at hairline and spreads downwards with sparing of palms and soles | Prodome of cough, coryza, conjunctivitis (3 Cs)<br>Enanthem: Koplik's spots 1-2 d before rash<br>Desquamation<br>Positive serology for measles IgM | Infected: supportive<br>Unimmunized contacts: measles vaccine within 72 h of exposure or IgG within 6 d of exposure<br>Respiratory isolation, report to Public Health<br>Prevention: MMR vaccine | Secondary bacterial infections: AOM, sinusitis, pneumonia<br>Encephalitis<br>Rare: myocarditis, pericarditis, thrombocytopenia, Stevens-Johnson syndrome, GN, subacute sclerosing panencephalitis |

**Table 24. Common Infectious Pediatric Exanthems** (continued)

| Disease | Pathogen(s) | Incubation Period | Communicability | Mode of Transmission | Rash | Associated Features | Management | Outcomes and Complications |
|---|---|---|---|---|---|---|---|---|
| **Non-Specific Enteroviral Exanthems** | Enteroviruses | Variable | Variable | Direct and indirect contact with infected bodily fluids | Polymorphous rash (macules, papules, vesicles, petechiae, urticaria) | Systemic involvement is rare, but possible | Supportive<br>Diagnosis confirmed using viral cultures (NP and rectal swabs) | Self-limiting |
| **Roseola** | HHV 6 | 5-15 d | Unknown | — | Appearance: blanching, pink, maculopapular<br>Timing: appears once fever subsides<br>Distribution: starts at the neck and trunk and spreads to the face and extremities | High grade fever<br>Common: irritability, anorexia, lymphadenopathy, erythematous TM and pharynx, Nagayama spots (erythematous papules on soft palate and uvula)<br>Less common: cough, coryza, bulging fontanelles | Supportive | CNS: febrile seizures (10-25%), aseptic meningitis<br>Thrombocytopenia |
| **Rubella** | Rubivirus | 14-21 d | 7 d before and after eruptions | Droplet | Appearance: pink, maculopapular<br>Timing: 1-5 d after start of symptoms<br>Distribution: starts on face and spreads to neck and trunk | Prodrome of low grade fever and occipital/retroauricular nodes<br>STAR complex (sore throat, arthritis, rash)<br>Positive serology for rubella IgM. Caution to pregnant women with expsoure | Infected: supportive<br>Prevention: MMR vaccine<br>Report to Public Health | Excellent prognosis with acquired disease<br>Arthritis may last days to weeks<br>Encephalitis<br>Irreversible defects in congenitally infected patients (i.e. congenital rubella syndrome) |
| **Scarlet Fever** | See P56 | | | | | | | |
| **Varicella** | Varicella zoster virus | 0-21 d | 1-2 d pre-eruptions and 5 d post-eruption | Mainly airborne, but also through direct contact with vesicle fluid | Appearance: groups of skin lesions, polymorphic, from macules to papules to vesicles to crusts<br>Timing: 1-3 d after start of symptoms<br>Distribution: generalized | Significant pruritis<br>Enanthem: vesicular lesions which may become pustular or ulcerate. Caution to pregnant women | Supportive<br>Avoid salicylates (due to risk of Reye syndrome)<br>Consider antivirals<br>Respiratory and contact isolation, report to Public Health<br>Prevention: varicella vaccine | Skin: bacterial suprainfection, necrotizing fasciitis<br>CNS: acute encephalitis and cerebellar ataxia<br>Systemic: hepatitis, DIC<br>Congenital varicella syndrome if intrapartum infection |

# Infectious Mononucleosis

### Definition
- systemic viral infection caused by EBV with multivisceral involvement; often called "the great imitator"

### Epidemiology
- peak incidence between 15-19 yr old
- ~50% of children in developed countries have a primary EBV infection by 5 yr old, but <10% of children develop clinical infection

### Etiology
- EBV: a member of herpesviridae
- transmission is mainly through infected saliva ("kissing disease") and sexual activity (less commonly); incubation period of 1-2 mo

### Risk Factors
- infectious contacts, sexually active, multiple sexual partners in the past

### History
- prodrome: 2-3 d of malaise, anorexia
- infants and young children: often asymptomatic or mild disease
- older children and adolescents: malaise, fatigue, fever, sore throat, abdominal pain (often LUQ), headache, myalgia

### Physical Exam
- classic triad: febrile, generalized non-tender lymphadenopathy, pharyngitis/tonsillitis (exudative)
- ± hepatosplenomegaly
- ± periorbital edema, ± rash (urticarial, maculopapular, or petechial) – more common after inappropriate treatment with β-lactam antibiotics
- any "-itis" (including arthritis, hepatitis, nephritis, myocarditis, meningitis, encephalitis, etc.)

### Investigations
- heterophil antibody test (Monospot® test)
  - 85% sensitive in adults and older children, but only 50% sensitive if <4 yr of age
  - false positive results with HIV, SLE, lymphoma, rubella, parvovirus
- EBV titres
- CBC and differential, blood smear: reactive lymphocytes, lymphocytosis, Downey cells ± anemia ± thrombocytopenia
- throat culture to rule out streptococcal pharyngitis

### Management
- supportive: adequate rest, hydration, saline gargles, and analgesics for sore throat
- splenic enlargement is often not clinically apparent so all patients should avoid contact sports for 6-8 wk
- if airway obstruction secondary to nodal and/or tonsillar enlargement is present (especially younger children), admit for steroid therapy
- acyclovir does NOT reduce duration of symptoms or result in earlier return to school/work

### Prognosis
- most acute symptoms resolve in 1-2 wk, though fatigue may last for months
- short-term complications: splenic rupture, Guillain-Barré syndrome

# Infectious Pharyngitis/Tonsillitis

### Definition
- inflammation of the pharynx, especially the tonsils if present, causing a sore throat

### Etiology
- viral (~80%): adenoviruses, enteroviruses, coxsackie, upper respiratory tract viruses, EBV, CMV
- bacterial (~20%): mainly GAS, *M. pneumoniae* (older children), *N. gonorrhoeae* (sexually active), *C. diphtheriae* (unvaccinated), *Fusobacterium necrophorum* (anaerobe causing Lemierre syndrome)
- fungal: *Candida*

### Epidemiology
- season: GAS pharyngitis more common in late winter or early spring; viral all year long
- age: GAS pharyngitis peak incidence at 5-12 yr of age and uncommon <3 yr; viral pharyngitis affects all ages

### Presentation
- GAS: sore throat (may be severe), febrile, malaise, headache, abdominal pain, N/V, absence of other URTI symptoms, pharyngeal/tonsillar serythema and exudates, enlarged (>1 cm) and tender anterior cervical lymph nodes, palatal petechiae, strawberry tongue, scarlatiniform rash
- viral: sore throat (often mild), afebrile, conjunctivitis, cough, rhinorrhea, hoarseness, diarrhea, flu-like symptoms (fever, malaise, myalgias), absent/mild tonsillar exudates, minor and non-tendor adenopathy, viral exanthems

### Investigations
- no single sign or symptom reliably identifies GAS as the causative organism in children with sore throat
- scores are used to predict if throat culture will be positive (e.g. m-CENTOR score)
  - these score systems have not been found to be sensitive or specific enough to diagnose GAS in children and adolescents with sore throat
- suspected diagnosis of GAS pharyngitis should be confirmed with a rapid streptococcal antigen test and a follow-up throat culture if the rapid test is negative



**m-CENTOR Score for Probability of Streptococcal Pharyngitis**
For patients presenting with sore throat/pharyngitis and URTI symptoms:
**M**ust be older than 3 years old
**C**ough — no Cough (+1)
**E**xudates or Swelling — tonsillar exudates/swelling (+1)
**N**odes — anterior Cervical adenopathy (+1)
**T**emperature — hx of fever or Temperature >38 (+1)
**O**nly Young — patients <15yo (+1)
**R**arely Elder — Patients >45 (-1)

### Management
- antibiotics (for GAS/*S. pyogenes*)
  - penicillin V or amoxicillin or erythromycin (if penicillin allergy) x 10 d
  - can prevent rheumatic fever if given within 9 d of symptoms; does NOT alter risk of post-streptococcal GN
- supportive: hydration and acetaminophen for discomfort due to pain and/or fever
- follow-up: if uncomplicated course, no follow-up or post-antibiotic throat cultures needed
- prophylaxis: consider tonsillectomy for proven, recurrent streptococcal tonsillitis

### Complications
- preventable with antibiotics: AOM, sinusitis, cervical adenitis, mastoiditis, retropharyngeal/peritonsillar abscess, sepsis
- immune-mediated complications: scarlet fever, acute rheumatic fever, post-streptococcal GN, reactive arthritis, pediatric autoimmune neuropsychiatric disorder associated with group A streptococci (i.e. PANDAS)

## SCARLET FEVER
- diffuse erythematous eruption
- delayed-type hypersensitivity reaction to pyrogenic exotoxin produced by GAS
- acute onset of fever, sore throat, strawberry tongue
- 24-48 h after pharyngitis, rash begins in the groin, axillae, neck, antecubital fossa; Pastia's lines may be accentuated in flexural areas
- within 24 h, sandpaper rash becomes generalized with perioral sparing, non-pruritic, non-painful, blanchable
- rash fades after 3-4 d, may be followed by desquamation
- treatment is penicillin, amoxicillin, or erythromycin x 10 d

## RHEUMATIC FEVER
- inflammatory disease due to antibody cross-reactivity following GAS infection
- affects ~1:10,000 children in developed world; much more prevalent in developing nations; peak incidence at 5-15 yr of age
- clinical diagnosis based on Jones Criteria (revised)
  - requires 2 major OR 1 major and 2 minor PLUS evidence of preceding strep infection (history of scarlet fever, GAS pharyngitis culture, positive rapid Ag detection test, ASOTs)
- treatment: penicillin or erythromycin for acute course x 10 d, prednisone if severe carditis
- secondary prophylaxis with daily penicillin or erythromycin
- complications
  - acute: myocarditis, conduction system aberrations (sinus tachycardia, atrial fibrillation), valvulitis (acute MR), pericarditis
  - chronic: valvular heart disease (mitral and/or aortic insufficiency/stenosis), infectious endocarditis ± thromboembolic phenomenon
  - onset of symptoms usually after 10-20 yr latency from acute carditis of rheumatic fever

## POST-STREPTOCOCCAL GLOMERULONEPHRITIS
- most common in children aged 4-8 yr old; M>F
- antigen-antibody mediated complement activation with diffuse, proliferative GN
- occurs 1-3 wk following initial GAS infection (skin or throat)
- clinical feature varies from asymptomatic, microscopic and macroscopic hematuria (cola-coloured urine) to all features of nephritic syndrome (see *Nephritic Syndrome*, P74)
- diagnosis is confirmed with elevated serum antibody titres against streptococcal antigens (ASOT, anti-DNAse B), low serum complement (C3)
- management
  - symptomatic: fluid and sodium restrictions; loop diuretics for HTN and edema
  - in severe cases, may require dialysis if renal function significantly impaired
  - treat with penicillin or erythromycin if evidence of persistent GAS infection
- 95% of children recover completely within 1-2 wk; 5-10% have persistent hematuria

# Meningitis

## Definition
- inflammation of the meninges surrounding the brain and spinal cord

## Epidemiology
- peak age: 6-12 mo; 90% of cases occur in children <5 yr old

## Etiology
- viral: enteroviruses, HSV
- bacterial: age-related variation in specific pathogens
- fungal and parasitic meningitis also possible
- most often due to hematogenous spread or direct extension from a contiguous site

## Risk Factors
- unvaccinated
- immunocompromised: asplenia, DM, HIV, prematurity
- recent or current infections: AOM, sinusitis, orbital cellulitis
- neuroanatomical: congenital defects, dermal sinus, neurosurgery, cochlear implants, recent head trauma
- exposures: daycare centres, household contact, recent travel

## History
- signs and symptoms variable and dependent on age, duration of illness, and host response to infection
- infants: fever, lethargy, irritability, poor feeding, vomiting, diarrhea, respiratory distress, seizures
- children: fever, headache, photophobia, N/V, confusion, back/neck pain/stiffness, lethargy, irritability

## Physical Exam
- infants: toxic, hypothermia, bulging anterior fontanelle, respiratory distress, apnea, petechial/purpuric rash, jaundice
- children: toxic, ↓ LOC, nuchal rigidity, Kernig's and Brudzinski's signs, focal neurologic findings, petechial/purpuric rash

## Investigations
- blood work: CBC, electrolytes, Cr, BUN, glucose, C&S
- LP required for definitive diagnosis
  - Gram stain, bacterial C&S, WBC count and differential, RBC count, glucose, protein concentration
  - acid-fast stain if suspect TB
  - PCR for specific bacteria if available (helpful if already treated with antibiotics)
  - urinalysis and urine C&S in infants, Gram stain and culture of petechial/purpuric lesions
  - HSV and enterovirus PCR if suspected

**Table 25. CSF Findings of Meningitis**

| Component | Normal Child | Normal Newborn | Bacterial Meningitis | Viral Meningitis | Herpes Meningitis | Tuberculosis Meningitis |
|---|---|---|---|---|---|---|
| WBC ($x10^6$/L) | ≤ 5 | 0-30 | Usually <100 | 10-1000 (can be normal) | 50-1000 (can be normal) | 100-500 |
| Neutrophils ($x10^6$/L) | | <20 | 100-10,000 (can be normal) | Usually <100 | Usually <100 | <30 |
| Glucose (CSF:Blood) | 0 | 0 | <0.4 (can be normal) | Usually normal | <0.3 (can be normal) | <0.5 |
| Protein (g/L) | ≥0.6 (or ≥2.5 mmol/L) | ≥0.6 (or ≥2.5 mmol/L) | >1.0 (can be normal) | 0.4-1.0 (can be normal) | 1-5 (Can be normal) | 0.5-0.8 |

Modified from https://www.rch.org.au/clinicalguide/guideline_index/CSF_Interpretation/

## Management
- supportive care
  - preservation of adequate cerebral perfusion by maintaining normal BP and managing ↑ ICP
  - close monitoring of fluids, electrolytes, glucose, acid-base disturbances, coagulopathies
- bacterial meningitis
  - if suspected or cannot be excluded, commence empiric antibiotic therapy while awaiting cultures or if LP contraindicated or delayed
  - adjuvant dexamethasone BEFORE antibiotic for Hib meningitis; consider for those >6 wk with pneumococcal meningitis
  - isolation with appropriate infection control procedures until 24 h after culture-sensitive antibiotic therapy
  - fluid restrict if any concern for SIADH
  - hearing test
  - report to Public Health; prophylactic antibiotics for close contacts of Hib and *N. meningitidis* meningitis

**Table 26. Antibiotic Management of Bacterial Meningitis**

| Age | Main Pathogens | Antibiotics |
|---|---|---|
| 0 to 28 d | GBS, *E. coli, Listeria*<br>Other: Gram-negative bacilli | Ampicillin + cefotaxime |
| 28 to 90 d | Overlap of neonatal pathogens and those seen in older children | Cefotaxime + vancomycin (+ Ampicillin If immunocompromised) |
| >90 d | *S. pneumoniae, N. meningitidis, H influenzae* | Ceftriaxone ± vancomycin<br>If Penicillin allergic: vancomycin + rifampin |



**Signs of Meningismus**

**BONK on the head**
**B**rudzinski's sign
**O**pisthotonos*
**N**uchal rigidity
**K**ernig's sign

*Opisthotonos: rigid spasm of the body, with the back fully arched and the heels and head bent back

- viral meningitis
  - mainly supportive (except for HSV)
  - acyclovir for HSV meningitis
  - report to Public Health
- prophylaxis: appropriate vaccinations significantly decrease incidence of bacterial meningitis (see *Routine Immunization*, P4)

### Complications
- mortality: neonate 15-20%, children 4-8%; pneumococcus > meningococcus > Hib
- acute: SIADH, subdural effusion/empyema, brain abscess, disseminated infection (osteomyelitis, septic arthritis, abscess), shock/DIC
- chronic: hearing loss, neuromotor/cognitive delay, learning disabilities, neurological deficit, seizure disorder, hydrocephalus

## Mumps

### Definition
- acute, self-limited viral infection that is most commonly characterized by adenitis and swelling of the parotid glands

### Epidemiology
- incidence in Ontario has declined since introduction of two-dose MMR vaccination schedule
- average of 25 reported cases per yr
- majority of reported cases in children between 5-10 yr of age

### Etiology
- mumps virus (RNA virus of the genus *Rubulavirus* in the *Paramyxoviridae* family)
- transmission via respiratory droplets, direct contact, fomites
- incubation period: 14-25 d
- infectivity period: 7 d pre-parotitis to 5 d post-parotitis
- upper respiratory tract, lymph nodes, salivary glands, gonads, pancreas, meninges, kidney, heart, thyroid

### History
- non-specific prodome of fever, headache, malaise, myalgias (especially neck pain)
- usually followed within 48 h by parotid swelling secondary to parotitis (bilateral, preauricular, ear pushed up and out)
- parotid gland is tender and pain worsened with spicy or sour foods
- one third of infections do not cause clinically apparent salivary gland swelling and may simply present as an URTI

### Investigations
- clinical diagnosis, but may be confirmed with IgM positive serology within 4 wk of acute infection
  - may also use PCR or viral cultures from oral secretions, urine, blood, and CSF
  - blood work: CBC (leukopenia with relative lymphocytosis), serum amylase (elevated)

### Management
- mainly supportive: analgesics, antipyretics, warm or cold packs to parotid may be soothing
- admit to hospital if serious complications (meningitis, pancreatitis)
- droplet precautions recommended until 5 d after onset of parotid swelling
- prophylaxis: routine vaccination (see *Routine Immunization*, P4)

### Complications
- common: aseptic meningitis, orchitis/oophoritis
- less common: encephalitis, pancreatitis, thyroiditis, myocarditis, arthritis, GN, ocular complications, hearing impairment

# Pertussis

### Definition
- prolonged respiratory illness characterized by paroxysmal coughing and inspiratory "whoop"

### Epidemiology
- ~10 million children <1 yr old affected worldwide, causes up to 400,000 deaths/yr
- greatest incidence among children <1 yr (not fully immunized) and adolescents (waning immunity)

### Etiology
- *Bordetella pertussis*: Gram negative pleomorphic rod
- highly contagious; transmitted via respiratory droplets released during intense coughing
- incubation period: 6-20 d; most contagious during catarrhal phase but may remain contagious for weeks after

### History
- prodromal catarrhal stage
  - lasts 1-7 d; URTI symptoms (coryza, mild cough, sneezing) with NO or low-grade fever
- paroxysmal stage
  - lasts 4-6 wk; characterized by paroxysms of cough ("100 day cough"), sometimes followed by inspiratory whoop ("whooping cough")
  - infants <6 mo may present with post-tussive apnea, whoop is often absent
  - onset of attacks precipitated by yawning, sneezing, eating, physical exertion
  - ± post-tussive emesis, may become cyanotic before whoop
  - vomiting after whooping episodes
- convalescent stage
  - lasts 1-2 wk; characterized by occasional paroxysms of cough, but decreased frequency and severity
  - non-infectious but cough may last up to 6 mo

### Investigations
- NP specimen using aspirate or NP swab
  - gold standard: culture using special media (Regan-Lowe agar)
  - PCR to detect pertussis antigens
- blood work: CBC (lymphocytosis) and serology (antibodies against *B. pertussis*)

### Management
- admit if paroxysms of cough are associated with cyanosis and/or apnea and give $O_2$
- supportive care
- antimicrobial therapy indicated if *B. pertussis* isolated, or symptoms present for <21 d
  - use macrolide antibiotics (azithromycin, erythromycin, or clarithromycin)
- droplet isolation until 5 d of treatment and report to Public Health
- prophylaxis
  - macrolide antibiotics for all household contacts
  - prevention with vaccination in infants and children (Pentacel®), and booster in adolescents (Adacel®) (see *Routine Immunization*, P4)

### Complications
- pressure-related from paroxysms: subconjunctival hemorrhage, rectal prolapse, hernias, epistaxis
- respiratory: sinusitis, pneumonia, aspiration, atelectasis, pneumomediastinum, pneumothorax, alveolar rupture
- neurological: seizures (~3%), encephalopathy, ICH
- mortality: ~0.3%; highest risk in infants <6 mo old

# Pneumonia

- see *Respirology*, P83

# Periorbital (Preseptal) and Orbital Cellulitis

- see Ophthalmology, OP9

**Cardinal Signs of Orbital Cellulitis**
- Ophthalmoplegia/diplopia
- Decreased visual acuity
- Pain with extraocular eye movement

# Sexually Transmitted Infections

- see Family Medicine, FM42 and Gynecology, GY26

# Sinusitis

- see Family Medicine, FM43
- complication of ≤10% of URTIs in children
- clinical diagnosis
- diagnostic imaging is NOT required to confirm diagnosis in children
  - routine CT not recommended, but consider if suspect complications of sinusitis, persistent/recurrent disease, need for surgery
- antibiotic therapy (Amoxicillin) for all children (although nearly half resolve spontaneously within 4 wk)
- complications: preseptal/orbital (preseptal/orbital cellulitis, orbital abscess, osteomyelitis, etc.), intracranial (meningitis, abscess, etc.), Pott's Puffy tumour (presents with tender soft tissue erythematous swelling of the forehead, symptoms include headache, photophobia, and fever; managed with IV antibiotics and ENT consult)

# Urinary Tract Infection

## Definition
- infection of the urinary bladder (cystitis) and/or kidneys (pyelonephritis)

## Epidemiology
- overall prevalence in infants and young children presenting with fever is 7%
- <4-6 wk old: more common in boys
- >1 yr old: females have two- to four-fold higher prevalence

## Etiology
- majority (>95%) have a single cause (~70% *E. coli*)
- Gram-negative bacilli: *E. coli, Klebsiella, Proteus, Enterobacter, Pseudomonas*
- Gram-positive cocci: *S. saprophyticus, Enterococcus*

## Risk Factors
- non-modifiable: female gender, Caucasian, previous UTIs, family history
- modifiable: urinary tract abnormalities (VUR, neurogenic bladder, obstructive uropathy, posterior urethral valve), dysfunctional voiding, repeated bladder catheterization, uncircumcised males, labial adhesions, sexually active, constipation, toilet training

## History
- infants and young child: often just fever or non-specific symptoms (poor feeding, irritability, FTT, jaundice if <28 d old, vomiting)
- older child: fever, urinary symptoms (dysuria, urgency, frequency, incontinence, hematuria), abdominal, and/or flank pain

## Physical Exam
- infants and young child: toxic vs. non-toxic, febrile, FTT, jaundice; look for external genitalia abnormalities (phimosis, labial adhesions) and lower back signs of occult myelodysplasia (e.g. hair tufts), which may be associated with neurogenic bladder
- older child: febrile, suprapubic and/or CVA tenderness, abdominal mass (enlarged bladder or kidney); may present with short stature, FTT, or HTN secondary to renal scarring from previously unrecognized or recurrent UTIs

## Investigations
- sterile urine specimen
  - clean catch, catheterization, suprapubic aspiration or 'Tap and Rub' technique
  - urinalysis (leukocyte esterase, nitrites, erythrocytes, hemoglobin), microscopy (bacteria and leukocytes, erythrocytes), C&S
- diagnosis established if urinalysis suggests infection AND if ≥50,000 colony-forming units per mL of a uropathogen cultured

**Features Suggestive of Pyelonephritis**
- High-grade fever
- Flank or high abdominal pain
- CVA tenderness on palpation

Bagged urine specimen not useful for ruling in UTI (high false positive rate >85%), but useful for ruling out UTI (high sensitivity)

## Management
- admit if: <2 mo old, urosepsis, persistent vomiting, inability to tolerate oral medication, moderate-severe dehydration, immunocompromised, complex urologic pathology, inadequate follow-up, failure to respond to outpatient therapy
- supportive care: maintenance of hydration and adequate pain control
- antibiotics
  - base on local antimicrobial susceptibility patterns
  - commence broad empiric therapy until results of urine C&S known, and then tailor as appropriate
  - neonates: IV ampicillin and gentamicin
  - infants and older children: oral antibiotics (based on local *E. coli* sensitivity) if outpatient; IV ampicillin and gentamicin if inpatient
  - duration 7-10 d
- imaging
  - renal and bladder U/S for all febrile infants (<2 yr) with UTIs looking for anatomical abnormalities, hydronephrosis, abscess
  - VCUG not recommended after 1st febrile UTI unless U/S reveals hydronephrosis, obstructive uropathies or other signs suggestive of high-grade VUR

**Prophylaxis After First Febrile Urinary Tract Infection in Children? A Multicentre, Randomized Controlled, Noninferiority Trial**
Pediatrics 2008;122:1064-1071
**Study:** Randomized, controlled, open-label, 2 armed, noninferiority trial.
**Patients:** 338 patients aged 2 mo to <7 yr who had a first episode of febrile UTI.
**Intervention:** No prophylaxis vs. prophylaxis.
**Outcome:** Recurrence rate of febrile UTI and rate of renal scarring.
**Results:** No significant difference in recurrence rate or in the rate of renal scarring between the prophylaxis and no prophylaxis group.

- follow-up: outpatients to return in 24-48 h if no clinical response and seek prompt medical evaluation for future febrile illnesses
- prophylaxis: generally not recommended unless higher grades of VUR

### Complications
- long-term morbidity: focal renal scarring develops in 8% of patients; long-term significance unknown

# Neonatology

## Gestational Age and Size

### Definitions
- classification by GA
  - preterm: <37 wk (extremely preterm <28 wk, very preterm 28-32 wk, moderate-late preterm 32-37 wk)
  - term: 37-42 wk
  - post-term: >42 wk
- classification by birth weight
  - SGA: 2 SD < mean weight for GA or <10th percentile
  - AGA: within 2 SD of mean weight for GA
  - LGA: 2 SD > mean weight for GA or >90th percentile
- classification of preterm infants by birth weight
  - low birthweight (LBW) <2500 g
  - very low birthweight (VLBW) <1500 g
  - extremely low birthweight (ELBW) <1000 g



**Dubowitz/Ballard Scores**
GA can be determined after birth using Dubowitz/Ballard scores:
- Assessment at delivery of physical maturity (e.g. plantar creases, lanugo, ear maturation) and neuromuscular maturity (e.g. posture, arm recoil) translates into a score from -10 to +50
- Higher score means greater maturity (increased GA)
- -10 = 20 wk; +50 = 44 wk
- Ideal = 35-40, which corresponds to GA 38-40 wk
- Only accurate ± 2 wk

**Table 27. Abnormalities of Gestational Age and Size**

| Features | Causes | Problems |
|---|---|---|
| **Pre-Term Infants**<br><37 wk | Spontaneous: cause unknown<br>Maternal disease: HTN, DM, cardiac and renal disorders<br>Fetal conditions: multiple pregnancy, congenital abnormalities, macrosomia, red blood cell isoimmunization, fetal infection<br>Pregnancy issues: placental insufficiency, placenta previa, uterine malformations, previous preterm birth, infection, placental abruption<br>Behavioural and psychological contributors: smoking, EtOH, drug use, psychosocial stressors<br>Sociodemographic factors: age, socioeconomic conditions | RDS, apnea of prematurity, chronic lung disease, bronchopulmonary dysplasia<br>Feeding difficulties, NEC<br>Hypocalcemia, hypoglycemia, hypothermia<br>Anemia, jaundice<br>Retinopathy of prematurity<br>ICH/IVH<br>PDA |
| **Post-Term Infants**<br>>42 wk<br>Leathery skin<br>Meconium staining | Most cases unknown<br>Increased in first pregnancies<br>Previous post-term birth<br>Genetic factors | Increased risk of stillbirth or neonatal death<br>Increased birthweight<br>Fetal "postmaturity syndrome": impaired growth due to placental dysfunction<br>Meconium aspiration |
| **SGA Infants**<br><10th percentile<br>Asymmetric (head-sparing): late onset, growth arrest | Extrinsic causes: placental insufficiency, poor nutrition, HTN, multiple pregnancies, drugs, EtOH, smoking | Perinatal hypoxia<br>Hypoglycemia, hypocalcemia, hypothermia, hyperviscosity (polycythemia), jaundice, hypomotility |
| Symmetric: early onset, lower growth | Intrinsic causes: maternal infections (TORCH), congenital abnormalities, syndromal, idiopathic | PDA |
| **LGA Infants**<br>>90th percentile | Maternal DM<br>Racial or familial factors<br>Increasing parity<br>Previous LGA infant, high BMI, large pregnancy weight gain<br>Certain syndromes | Birth trauma, perinatal depression (meconium aspiration)<br>RDS, TTN<br>Jaundice, polycythemia<br>Hypoglycemia, hypocalcemia |

## Routine Neonatal Care

- history taking
  - passage of meconium in 24-48 h, urination/number of wet diapers
  - feeding: breast milk or formula, route (breast or bottle), duration, frequency and volume of feeds
  - issues: jaundice, poor feeding, difficulty breathing, cyanosis, seizures
  - weight: discharge weight (close follow-up if >10% below birth weight), initial weight gain (goal 20-25 g/d), number of days until birth weight regained (should regain by day 10 of life)
- erythromycin ointment: applied to both eyes for prophylaxis of ophthalmia neonatorum (of questionable efficacy)
- vitamin K IM: prophylaxis against HDNB
- newborn screening tests in Ontario
  - in Ontario, newborn screening tests for:
    - metabolic disorders (amino acid disorders, organic acid disorders, fatty acid oxidation defects, biotinidase deficiency, galactosemia)
    - blood disorders (SCD, other hemoglobinopathies)
    - endocrine disorders (CAH, congenital hypothyroidism)
    - others (CF, severe combined immunodeficiency)
    - congenital hearing loss
- if mother Rh negative: send cord blood for blood group and direct antiglobulin test
- if household contact is hepatitis B surface antigen positive: start hepatitis B vaccine series (and if mother is positive, give HBIg within 12 h of birth)

# Neonatal Resuscitation

- assess Apgar score at 1 and 5 min
- if <7 at 5 min then reassess q5min, until >7
- do not wait to assign Apgar score before initiating resuscitation

**Apgar Score**
**A**ppearance (colour)
**P**ulse (heart rate)
**G**rimace (irritability)
**A**ctivity (tone)
**R**espiration (respiratory effort)
Or: "How Ready Is This Child?"

**Table 28. Apgar Score**

| Sign | 0 | 1 | 2 |
|---|---|---|---|
| Heart Rate | Absent | <100/min | >100/min |
| Respiratory Effort | Absent | Slow, irregular | Good, crying |
| Irritability | No response | Grimace | Cough/cry |
| Tone | Limp | Some flexion of extremities | Active motion |
| Colour | Blue, pale | Body pink, extremities blue (acrocyanosis) | Completely pink |

## Initial Resuscitation

- anticipation: know maternal history, history of pregnancy, labour, and delivery
- steps to take for all infants
  - pre-delivery team debriefing including assigning roles, checking equipment, and discussing possible complications and management plan
  - warm (radiant heater, warm blankets) and dry the newborn (remove wet blankets)
  - stimulate infant: rub lower back gently or flick soles of feet
  - position airway ("sniffing" position) and clear or suction if necessary
  - assess breathing and heart rate
  - if no response to stimulation: bag and mask ventilation. Continue until HR >100 and breathing spontaneously
  - if HR <60: establish effective ventilation and start chest compressions
  - if meconium present: a team with advanced resuscitation skills should be present. If the newborn is hypotonic with ineffective respirations, routine intubation for tracheal suction is not suggested. Do initial resuscitation and administer PPV as required

**Use of 100% Oxygen in Neonatal Resuscitation**
Circulation 2015;132(suppl 2):S543–S560
Findings from animal and theoretical studies have suggested potential adverse effects with the administration of 100% oxygen. However, given available data is limited in general and only obtained from newborn samples, the 2015 neonatal resuscitation guidelines have provided the following recommendation: "Since an oxygen saturation of 100% may correspond to a $PaO_2$ anywhere between ~80 and 500 mm Hg, in general it is appropriate to wean the $FIO_2$ for a saturation of 100%, provided the oxyhemoglobin saturation can be maintained ≥94%." (Class IIb, LOE C).

**Table 29. Interventions Used in Neonatal Resuscitation**

| Intervention | Schedule | Indications | Comments |
|---|---|---|---|
| **Epinephrine** (adrenaline) | 0.1-0.3 mL/kg/dose of 1:10,000 (0.01-0.03 mg/kg) IV<br>0.5-1 mL/kg/dose of 1:10,000 (0.05-0.1 mg/kg) endotracheally can be considered while awaiting IV access (IV preferred)<br>Can be repeated q3-5 min prn | HR <60 and not rising | Side effects: tachycardia, HTN, cardiac arrhythmias |
| **Fluid Bolus** (NS, whole blood, Ringer's lactate) | 10 mL/kg<br>May need to be repeated<br>Avoid giving too rapidly as large volume rapid infusions can be associated with IVH | Evidence of hypovolemia | |

**Corrective Actions for PPV in Neonatal Resuscitation**

**MR SOPA**
**M**ask readjustment
**R**eposition airway
**S**uction mouth and nose
**O**pen mouth
**P**ressure increase
**A**lternative airway

## Approach to the Depressed Newborn

- a depressed newborn lacks one or more of the following characteristics of a normal newborn
  - pulse >100 bpm
  - cries when stimulated
  - actively moves all extremities
  - has a good strong cry
- approximately 10% of newborn babies require assistance with breathing after delivery

**Table 30. Etiology of Respiratory Depression in the Newborn**

| Etiology | Examples |
|---|---|
| **Respiratory Problems** | RDS/hyaline membrane disease<br>Pulmonary hypoplasia<br>CNS depression<br>MAS<br>Pneumonia<br>Pneumothorax<br>Pleural effusions<br>Congenital malformations |
| **Anemia** (severe) | Erythroblastosis fetalis<br>Secondary hydrops fetalis |
| **Maternal Causes** | Drugs/anesthesia (opiates, magnesium sulphate)<br>DM<br>Maternal myasthenia gravis |
| **Congenital Malformations/Birth Injury** | Nuchal cord, perinatal depression<br>Bilateral phrenic nerve injury<br>Potter's sequence |
| **Shock** | Antepartum hemorrhage |
| **CHD** | Transposition of the great arteries with intact ventricular septum |
| **Other** | Hypothermia<br>Hypoglycemia<br>Infection |

**Targeted Preductal $SpO_2$ After Birth**

| | |
|---|---|
| 1 min | 60-65% |
| 2 min | 65-70% |
| 3 min | 70-75% |
| 4 min | 75-80% |
| 5 min | 80-85% |
| 10 min | 85-95% |

### Diagnosis
- vital signs including pre- and post-ductal oxygen saturations and 4 limb blood pressure
- detailed maternal history: include prenatal care, illnesses, use of drugs, previous high risk pregnancies, infections during pregnancy (including GBS status), duration of ruptured membranes, maternal fever or signs of chorioamnionitis during labour/delivery, blood type and Rh status, amniotic fluid status, GA, meconium, Apgar scores
- clinical findings (observe for signs of respiratory distress such as cyanosis, tachypnea, retractions, grunting, temperature instability)
- laboratory results (CBC, blood gas, blood type and DAT, glucose)
- transillumination of chest to evaluate for pneumothorax
- CXR, ECG, echocardiogram

### Management
- see *Neonatal Resuscitation*, P62, identify and treat underlying cause

# Common Conditions of Neonates

## Apnea

### Definition
- periodic breathing: normal respiratory pattern seen in newborns in which periods of rapid respiration are alternated with pauses lasting 5-10 s
- apnea: absence of respiratory gas flow for >20 s (or less if associated with bradycardia or desaturation)
- three types of apnea
  - central: no chest wall movement, no signs of obstruction
  - obstructive: chest wall movement continues against obstructed upper airway, no airflow
  - mixed: combination of central and obstructive apnea

### Differential Diagnosis
- in term infants, apnea requires full septic workup (CBC and differential, blood and urine cultures ± LP, CXR)
- other causes
  - CNS: seizures, ICH
  - apnea of prematurity (<34 wk): combination of CNS immaturity and obstructive apnea; resolves by 36 wk GA; diagnosis of exclusion
  - hypoxic injury
  - infectious: sepsis, meningitis, NEC
  - GI: GERD, aspiration with feeding
  - metabolic: hypoglycemia, hyponatremia, hypocalcemia, inborn error of metabolism
  - cardiovascular: anemia, hypovolemia, PDA, heart failure
  - medications: morphine

### Management
- $O_2$, ventilatory support, maintain normal blood gases
- tactile stimulation
- correct underlying cause
- medications: methylxanthines (caffeine) stimulate the CNS and diaphragm and are used for apnea of prematurity (not in term infants)
- if apnea of prematurity is diagnosed, infants should receive cardiorespiratory monitoring in a neonatal intensive care unit

## Bleeding Disorders in Neonates

### Clinical Feature
- oozing from the umbilical stump, excessive bleeding from peripheral venipuncture/heel stick sites/IV sites, large caput succedaneum, cephalohematomas (in absence of significant birth trauma), subgaleal hemorrhage and prolonged bleeding following circumcision

### Etiology
- 4 major categories
  - increased platelet destruction: maternal ITP or SLE, infection/sepsis, DIC, neonatal alloimmune thrombocytopenia, autoimmune thrombocytopenia
  - decreased platelet production/function: pancytopenia, bone marrow replacement, Fanconi anemia, Trisomy 13 and 18
  - metabolic: congenital thyrotoxicosis, inborn error of metabolism
  - coagulation factor deficiencies (see Hematology, H53): hemophilia A/B, HDNB

### NEONATAL ALLOIMMUNE THROMBOCYTOPENIA

#### Epidemiology
- 1 per 4000-5000 live births

#### Pathophysiology
- platelet equivalent of Rh disease of the newborn
- occurs when mother is negative for HPA and fetus is positive
- development of maternal IgG antibodies against HPA antigens on fetal platelets

#### Clinical Feature
- petechiae, purpura, thrombocytopenia in otherwise healthy neonate
- severe disease can lead to intracranial bleeding

#### Diagnosis
- maternal and paternal platelet typing and identification of platelet alloantibodies

#### Treatment
- IVIg to mother prenatally starts in second trimester ± steroids ± fetal platelet transfusions
- if transfusion required, use washed maternal platelets or donor HPA negative platelets
- treat neonate with IVIg (less effective than platelet transfusions)

### AUTOIMMUNE THROMBOCYTOPENIA

#### Pathophysiology
- caused by antiplatelet antibodies from maternal ITP or SLE
- passive transfer of antibodies across placenta

#### Clinical Feature
- similar presentation to neonatal alloimmune thrombocytopenia, but thrombocytopenia usually less severe

#### Treatment
- steroids to mother for 10-14 d prior to delivery or IVIg to mother before delivery
- treat neonate with IVIg (usually if platelets <60,000)
- transfusion of infant with maternal/donor platelets only in severe cases, as antibodies will destroy transfused platelets

### HEMORRHAGIC DISEASE OF THE NEWBORN

#### Pathophysiology
- caused by vitamin K deficiency
- factors II, VII, IX, X are vitamin K-dependent, therefore both PT and PTT are abnormal

#### Etiology and Clinical Feature
- neonates at increased risk of vitamin K deficiency due to:
  - poor transfer of vitamin K across the placenta
  - insufficient bacterial colonization of colon at birth to synthesize vitamin K
  - breastfeeding (inadequate vitamin K intake)
  - additional risk if maternal use of antiepileptics
- neonate may present with hematomas, ICH (causing apnea or seizures), internal bleeding, hematuria, bruising, prolonged bleeding (often from mucous membranes, umbilicus, circumcision, and venipunctures)

#### Prevention
- vitamin K IM administration at birth to all newborns

## Bronchopulmonary Dysplasia

#### Definition
- also known as chronic lung disease
- clinically defined as $O_2$ requirement for >28 d plus persistent need for oxygen and/or ventilatory support at 36 wk corrected GA
- damage to developing lungs with prolonged intubation/ventilation, high levels $O_2$, infections

#### Investigations
- CXR findings may demonstrate decreased lung volumes, areas of atelectasis, signs of inflammation, and hyperinflation

### Treatment
- no good treatments
- gradual wean from ventilator, optimize nutrition
- dexamethasone may help decrease inflammation and encourage weaning, but use of dexamethasone is associated with increased risk of adverse neurodevelopmental outcomes

### Prognosis
- chronic respiratory failure may lead to pulmonary HTN, poor growth, and right-sided heart failure
- patients with bronchopulmonary dysplasia may continue to have significant impairment and deterioration in lung function late into adolescence
- some lung abnormalities may persist into adulthood including airway obstruction, airway hyperreactivity, and emphysema
- associated with increased risk of adverse neurodevelopmental outcomes

## Cyanosis

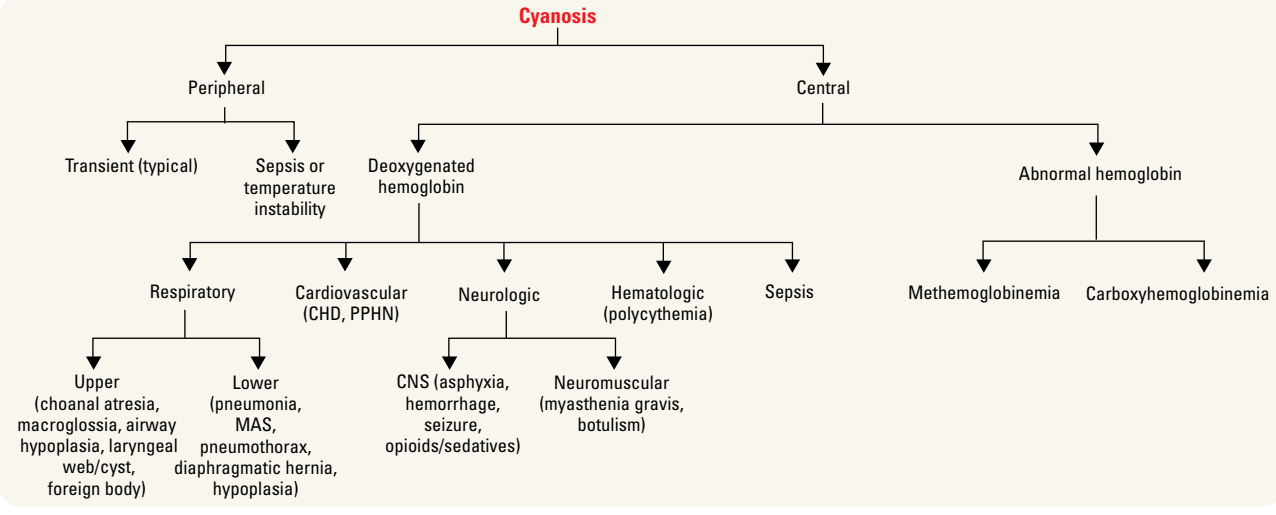



**Figure 14. Approach to neonatal cyanosis**

### Management
- ABGs
  - elevated $CO_2$ suggests respiratory cause
  - hyperoxia test (to distinguish between cardiac and respiratory causes of cyanosis): get baseline $PaO_2$ in room air, then $PaO_2$ on 100% $O_2$ for 10-15 min
    - $PaO_2$ <150 mmHg: suggests cyanotic CHD or possible PPHN (see *Cardiology*, P20)
    - $PaO_2$ >150 mmHg: suggests cyanosis likely due to respiratory or non-cardiac cause
- CXR: look for respiratory abnormalities (pneumothorax, respiratory tract malformations, evidence of shunting, pulmonary infiltrates) and cardiac abnormalities (cardiomegaly, abnormalities of the great vessels)

**Carboxyhemoglobinemia** (secondary to carbon monoxide poisoning) results in impaired binding of oxygen to hemoglobin but does not discolour the blood. Therefore it may not register on pulse oximetry and cyanosis may not be evident clinically

**Methemoglobinemia** typically reads higher on pulse oximetry than the true level of oxyhemoglobin. Methemoglobin alters the absorption of red light at the two wavelengths that pulse oximetry uses to predict oxygen saturation

## Diaphragmatic Hernia

- see General Surgery, GS67

### Definition
- developmental defect of the diaphragm with herniation of abdominal organs into thorax
- associated with pulmonary hypoplasia and PPHN

### Clinical Feature
- respiratory distress, cyanosis
- scaphoid abdomen and barrel-shaped chest
- affected side dull to percussion and breath sounds absent, may hear bowel sounds instead
- heart sounds shifted to contralateral side
- asymmetric chest movements, trachea deviated away from affected side
- may present outside of neonatal period
- often associated with other anomalies (cardiovascular, CNS, chromosomal abnormalities)
- CXR: bowel loops in thorax (usually left side), displaced mediastinum

### Treatment
- immediate intubation required at birth: DO NOT bag mask ventilate because air will enter stomach and further compress lungs
- place large bore orogastric tube to decompress bowel
- initial stabilization and management of pulmonary hypoplasia and PPHN if present, hemodynamic support and surgery when stable

## Hypoglycemia

### Definition
- glucose <2.6 mmol/L

### Etiology
- decreased carbohydrate stores: premature, SGA, RDS, maternal HTN
- endocrine: hormonal deficiencies (GH, cortisol, epinephrine), insulin excess (infant of diabetic mother, Beckwith-Wiedemann syndrome/islet cell hyperplasia), HPA axis suppression (panhypopituitarism)
- inborn errors of metabolism: fatty acid oxidation defects, galactosemia
- miscellaneous: sepsis, hypothermia, polycythemia

### Clinical Findings
- signs often non-specific and subtle: lethargy, poor feeding, irritability, tremors, apnea, cyanosis, seizures

### Management
- identify and monitor infants at risk (pre-feed blood glucose checks) until blood glucose stable and for at least 12 h (for infant of diabetic mother or LGA) or 36 h (if preterm or SGA)
- begin oral feeds as soon as possible after birth and ensure regular feeds
- if significant and/or symptomatic hypoglycemia, provide glucose IV and titrate according to blood sugar levels
- if persistent hypoglycemia or no predisposing cause, send "critical blood work" during an episode of hypoglycemia: ABG, ammonia, β-hydroxybutyrate, cortisol, free fatty acids, GH, insulin, lactate, urine dipstick for ketones

## Neonatal Hyperbilirubinemia

### Definition
- total serum bilirubin >95th percentile (high risk zone) on Bhutani nomogram in infants >35 wk GA

### Clinical Feature
- jaundice typically visible at serum bilirubin levels of 85-120 μmol/L
- visual assessment is often misleading and should confirm with blood test

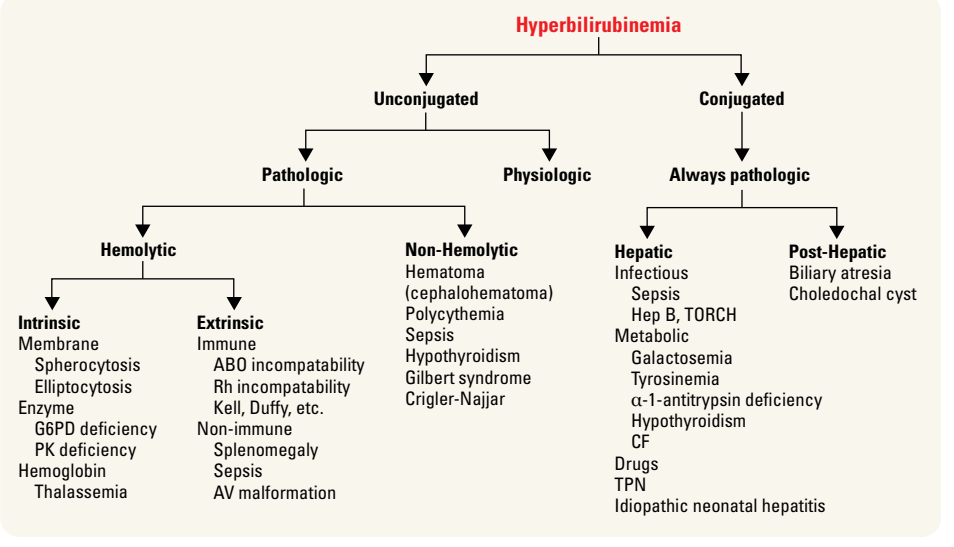



**Figure 15. Approach to neonatal hyperbilirubinemia**

Jaundice is very common – 60% of term newborns develop visible jaundice

Jaundice in the first 24 h of life and conjugated hyperbilirubinemia are always pathological

**Jaundice must be investigated if:**
- It occurs within 24 h of birth
- Conjugated hyperbilirubinemia is present
- Unconjugated bilirubin rises rapidly or is excessive for patient's age and weight
- Persistent jaundice lasts beyond 1-2 wk of age

## PHYSIOLOGIC JAUNDICE

### Epidemiology
- term infants: onset 3-4 d of life, resolution by 10 d of life
- premature infants: higher peak and longer duration

### Pathophysiology
- increased hematocrit and decreased RBC lifespan
- immature glucuronyl transferase enzyme system (slow conjugation of bilirubin)
- increased enterohepatic circulation

### Breastfeeding Jaundice
- common: due to a lack of milk production → dehydration → exaggerated physiologic jaundice

### Breast Milk Jaundice
- 1 per 200 breastfed infants
- glucuronyl transferase inhibitor found in breast milk
- onset 7 d of life, peak at 2-3 wk of life, usually resolved by 6 wk

**Table 31. Risk Factors for Jaundice**

| Maternal Factors | Perinatal Factors | Neonatal Factors |
|---|---|---|
| Ethnic group (e.g. Asian, Indigenous)<br>Complications during pregnancy (infant of diabetic mother, Rh or ABO incompatibility)<br>Breastfeeding<br>Family history/previous child required phototherapy | Birth trauma (cephalohematoma, ecchymoses)<br>Prematurity | Difficulty establishing breastfeeding<br>Infection (sepsis, hepatitis)<br>Genetic factors<br>Polycythemia<br>Drugs<br>TPN |

**Table 32. Causes of Neonatal Jaundice by Age**

| <24 h | 24-72 h | 72-96 h | Prolonged (>1 wk) |
|---|---|---|---|
| **ALWAYS PATHOLOGIC**<br>Hemolytic<br>Rh or ABO incompatibility<br>Sepsis<br>Congenital infection (TORCH)<br>Severe bruising/hemorrhage | Physiologic, polycythemia<br>Dehydration (breastfeeding jaundice)<br>Hemolysis<br>G6PD deficiency<br>Pyruvate kinase deficiency<br>Spherocytosis<br>Bruising, hemorrhage, hematoma<br>Sepsis/congenital infection | Physiologic ± breastfeeding<br>Sepsis | Breast milk jaundice<br>Prolonged physiologic jaundice in preterm<br>Hypothyroidism<br>Neonatal hepatitis<br>Conjugation dysfunction e.g. Gilbert syndrome, Crigler-Najjar syndrome<br>Inborn errors of metabolism e.g. galactosemia<br>Biliary tract obstruction e.g. biliary atresia |

## PATHOLOGIC JAUNDICE
- all cases of conjugated hyperbilirubinemia; some cases of unconjugated hyperbilirubinemia are pathologic

### Investigations
- unconjugated hyperbilirubinemia
  - hemolytic workup: CBC, reticulocyte count, blood group (mother and infant), peripheral blood smear, Coombs test
  - if baby is unwell or has fever: septic workup (CBC and differential, blood and urine cultures ± LP, CXR)
  - other: G6PD screen (especially in males), TSH
- conjugated hyperbilirubinemia must be investigated without delay
  - consider liver enzymes (AST, ALT), coagulation studies (PT, PTT), serum albumin, ammonia, TSH, TORCH screen, septic workup, galactosemia screen (erythrocyte galactose-1-phosphate uridyltransferase levels), metabolic screen, abdominal U/S, HIDA scan, sweat chloride
- predicting occurrence of severe hyperbilirubinemia
  - measure either TSB or TcB concentration in all infants between 24 h and 72 h of life and plot on appropriate hyperbilirubinemia treatment graph. If infant does not require immediate treatment, results should be plotted on predictive nomogram to determine the risk of progression to severe hyperbilirubinemia and need for repeat measurement (refer to: http://www.cps.ca/documents/position/hyperbilirubinemia-newborn)

## TREATMENT OF UNCONJUGATED HYPERBILIRUBINEMIA

- to prevent kernicterus
- breastfeeding does not usually need to be discontinued, ensure adequate feeds and hydration
- lactation consultant support, mother to pump after feeds
- treat underlying causes (e.g. sepsis)
- phototherapy (blue-green wavelength, not UV light) – standard intensive or multiple intensive protocol depending on severeity of hyperbilirubinemia
  - insoluble unconjugated bilirubin is converted to excretable form via photoisomerization
  - serum bilirubin should be monitored during and immediately after therapy (risk of rebound because photoisomerization reversible when phototherapy discontinued)
  - contraindicated in conjugated hyperbilirubinemia: results in "bronzed" baby
  - side effects: skin rash, diarrhea, eye damage (eye shield used routinely for prevention), dehydration
  - use published guidelines and nomogram for initiation of phototherapy
- exchange transfusion
  - indications: high bilirubin levels as per published graphs based on age, weeks gestation
  - most commonly performed for hemolytic disease and G6PD deficiency
  - use of IVIg in case of severe hyperbilirubinemia (DAT+) becoming evidence-based practice



"Bronzed" Baby in Infants with Conjugated Hyperbilirubinemia
Phototherapy results in the production and accumulation of a toxic metabolite which also imparts a bronze hue on the baby's skin

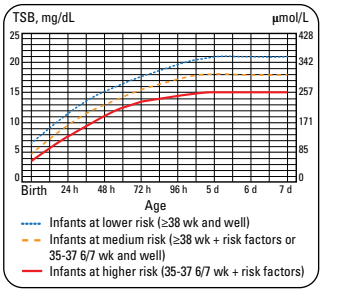



**Figure 16. Gold standard in deciding when to initiate phototherapy for unconjugated hyperbilirubinemia**
Licence number: 4601410094382

## KERNICTERUS

### Etiology

- unconjugated bilirubin concentrations exceed albumin binding capacity and bilirubin is deposited in the brain resulting in tissue necrosis and permanent damage (typically basal ganglia or brainstem)
- incidence increases as serum bilirubin levels increase above 340 µmol/L
- can occur at lower levels in presence of sepsis, meningitis, hemolysis, hypoxia, acidosis, hypothermia, hypoglycemia, and prematurity

### Clinical Feature

- up to 15% of infants have no obvious neurologic symptoms
- early stage: lethargy, hypotonia, poor feeding, emesis (bilirubin encephalopathy)
- mid stage: hypertonia, high pitched cry, opisthotonic posturing (back arching), bulging fontanelle, seizures, pulmonary hemorrhage
- late stage (during first year and beyond)
  - hypotonia, delayed motor skills, extrapyramidal abnormalities (choreoathetoid CP), gaze palsy, mitral regurgitation, sensorineural hearing loss

### Prevention

- exchange transfusion, IVIg if indicated

## BILIARY ATRESIA

### Definition

- atresia of the extrahepatic bile ducts which leads to cholestasis and increased conjugated bilirubin after the first wk of life
- progressive obliterative cholangiopathy

### Epidemiology

- incidence: 1:10,000-15,000 live births
- associated anomalies in 10-35% of cases: situs inversus, congenital heart defects, polysplenia

### Clinical Feature

- dark urine, pale stool, jaundice (persisting for >2 wk), abdominal distension, hepatomegaly

### Diagnosis

- conjugated hyperbilirubinemia, abdominal U/S, operative cholangiogram
- HIDA scan (may be bypassed in favour of biopsy if timing of diagnosis is critical)
- liver biopsy

### Treatment

- surgical drainage procedure
- hepatoportoenterostomy (Kasai procedure; most successful if <8 wk of age)
- two-thirds will eventually require liver transplantation
- vitamins A, D, E, and K; diet should be enriched with medium-chain triglycerides to ensure adequate fat ingestion

# Necrotizing Enterocolitis

### Definition
- intestinal inflammation associated with focal or diffuse ulceration and necrosis
- primarily affecting terminal ileum and colon

### Epidemiology
- affects 1-5% of preterm newborns admitted to NICU

### Pathophysiology
- postulated mechanism of bowel ischemia: mucosal damage and enteral feeding → bacterial growth → bowel necrosis/gangrene/perforation

### Risk Factors
- prematurity (immature defenses)
- asphyxia, shock (poor bowel perfusion)
- hyperosmolar feeds
- enteral feeding with formula (breast milk can be protective)
- sepsis

### Clinical Feature
- usually presents at 2-3 wk of age
- distended abdomen, diminished bowel sounds, feeding intolerance
- increased amount of gastric aspirate/vomitus with bile staining
- frank or occult blood in stool
- signs of bowel perforation (sepsis, shock, peritonitis, DIC)

### Investigations
- AXR: pneumonitis intestinalis (intramural air is a hallmark of NEC), free air, fixed loops, ileus, thickened bowel wall, portal venous gas
- CBC, ABG, lactate, blood culture, electrolytes
- high or low WBC, low platelets, hyponatremia, acidosis, hypoxia, hypercapnea

### Treatment
- NPO (7-10 d), vigorous IV fluid resuscitation, decompression with NG tube, supportive therapy
- TPN
- antibiotics (usually ampicillin, gentamicin ± metronidazole if risk of perforation x 7-10 d)
- serial AXRs detect early perforation (40% mortality in perforated NEC)
- peritoneal drain/surgery if perforation
- surgical resection of necrotic bowel and surgery for complications (e.g. perforation, strictures)

**Influence of Enteral Nutrition on Occurrences of Necrotizing Enterocolitis in Very-Low-Birth-Weight Infants**
J Pediatr Gastroenterol Nutr 2015;61(4):445-50
**Study**: Case-control study of very-low-birth-weight (VLBW) infants and occurrences of NEC within 30 d of life.
**Population**: 1028 VLBW infants in neonatal intensive care unit Jan 2003-May 2008.
**Main Outcome**: NEC defined using stage ≥2 of modified Bell criteria.
**Results**: 55 infants developed NEC within 30 d of life (5.4%). Those with NEC had higher odds of having been fed breast milk <7 d (OR: 4.02), not having achieved full enteral feeding during the first mo (OR: 3.50), and having had parenteral feeding (OR: 2.70).
**Conclusions**: Occurrence of NEC can be reduced with breast milk feeding beyond 7 d and early full enteral feeding.

# Persistent Pulmonary Hypertension of the Newborn

### Definition
- persistence of fetal circulation as a result of persistent elevation of pulmonary vascular resistance
- classified as primary (absence of risk factors) or secondary

### Epidemiology
- incidence 1.9/1000 live births

### Clinical Feature
- usually presents within 12 h of birth with severe hypoxemia/cyanosis; may have only mild respiratory distress

### Pathophysiology
- elevated pulmonary pressures cause R → L shunt through PDA, foramen ovale → decreased pulmonary blood flow and hypoxemia → further pulmonary vasoconstriction

### Risk Factors
- secondary PPHN: asphyxia, meconium aspiration syndrome, RDS, sepsis, pneumonia, structural abnormalities (e.g. diaphragmatic hernia, pulmonary hypoplasia)
- more common in term or post-term infants

### Investigations
- measure pre- and post-ductal oxygen levels
- hyperoxia test to exclude CHD
- ECG (RV strain)
- Echo reveals increased pulmonary arterial pressure and a R → L shunt across PDA and patent foramen ovale; also used to rule out other cardiac defects

### Treatment
- maintain good oxygenation ($SaO_2$ >95%) in at-risk infants
- $O_2$ given early and tapered slowly, minimize stress and metabolic demands, maintain normal blood gases, circulatory support
- mechanical ventilation, high frequency oscillation in a sedated muscle-relaxed infant
- nitric oxide, surfactant
- extracorporeal membrane oxygenation used in some centres when other therapy fails

## Respiratory Distress in the Newborn

### Clinical Feature
- tachypnea: RR >60/min; tachycardia: HR >160/min
- grunting, subcostal/intercostal indrawing, nasal flaring
- duskiness, central cyanosis
- decreased air entry, crackles on auscultation

### Differential Diagnosis of Respiratory Distress
- see Table 30 under Neonatal Resuscitation

### Investigations
- labs: CBC, blood gas, glucose, blood culture
- imaging: CXR
- if indicated: ECG, Echo, LP (CSF cell count, culture, and chemistry)

**Table 33. Distinguishing Features of RDS, TTN, MAS**

| | RDS | TTN | MAS |
|---|---|---|---|
| **Etiology** | Surfactant deficiency → poor lung compliance due to high alveolar surface tension → atelectasis → ↓ surface area for gas exchange → hypoxia + acidosis → respiratory distress<br>"Hyaline membrane disease" | Delayed resorption of fetal lung fluid → accumulation of fluid in peribronchial lymphatics and vascular spaces → tachypnea<br>"Wet lung syndrome" | Meconium is sterile but causes airway obstruction, chemical inflammation, and surfactant inactivation leading to chemical pneumonitis |
| **Gestational Age** | Preterm | Usually term and late preterm | Term and post-term |
| **Risk Factors** | Maternal DM<br>Preterm delivery<br>Male sex<br>LBW<br>Acidosis, sepsis<br>Hypothermia<br>Second born twin | Maternal DM<br>Maternal asthma<br>Male sex<br>Macrosomia (>4500 g)<br>Elective Cesarean section or short labour<br>Late preterm delivery | Meconium-stained amniotic fluid<br>Post-term delivery |
| **Clinical Feature** | Respiratory distress within first few hours of life, worsens over next 24-72 h<br>Hypoxia<br>Cyanosis | Tachypnea within the first few hours of life ± retractions, grunting, nasal flaring<br>Often NO hypoxia or cyanosis | Respiratory distress within hours of birth<br>Small airway obstruction, chemical pneumonitis tachypnea, barrel chest with audible crackles<br>Hypoxia |
| **CXR Findings** | Homogenous infiltrates<br>Air bronchograms<br>Decreased lung volumes<br>May resemble pneumonia (GBS)<br>If severe, "white-out" with no differentiation of cardiac border | Perihilar infiltrates<br>"Wet silhouette"; fluid in fissures | Hyperinflation<br>Patchy atelectasis<br>Patchy and coarse infiltrates<br>10-20% have pneumothorax |
| **Prevention** | Prenatal corticosteroids (e.g. Celestone® 12 mg q24h x 2 doses) if risk of preterm delivery <34 wk<br>Monitor lecithin:sphingomyelin (L/S) ratio with amniocentesis, L/S >2:1 indicates lung maturity | Where possible, avoidance of elective Cesarean delivery, particularly before 38 wk GA | If infant is depressed at birth, intubate and suction below vocal cords<br>Avoidance of factors associated with *in utero* passage of meconium (e.g. post term delivery) |
| **Treatment** | Resuscitation<br>Oxygen<br>Ventilation<br>Surfactant (decreases alveolar surface tension, improves lung compliance, and maintains functional residual capacity) | Supportive<br>Oxygen if hypoxic<br>Ventilator support (e.g. CPAP)<br>IV fluids and NG tube feeds if too tachypneic to feed orally | Resuscitation<br>Oxygen<br>Ventilatory support<br>Surfactant<br>Inhaled nitric oxide<br>Extracorporeal membrane oxygenation for PPHN |
| **Complications** | In severe prematurity and/or prolonged ventilation, increased risk of bronchopulmonary dysplasia | Hypoxemia<br>Hypercapnea<br>Acidosis<br>PPHN | Hypoxemia<br>Hypercapnea<br>Acidosis<br>PPHN<br>Pneumothorax<br>Pneumomediastinum<br>Chemical pneumonitis<br>Secondary surfactant inhibition<br>Respiratory failure |
| **Prognosis** | Dependent on GA at birth and severity of underlying lung disease; long-term risks of chronic lung disease | Recovery usually expected in 24-72 h | Dependent on severity, mortality up to 20% |

### PNEUMONIA

- see *Respirology*, P83
- consider in infants with prolonged (≥18 h) or premature rupture of membranes, maternal fever or other signs and symptoms of chorioamnionitis, or if mother is GBS positive
- suspect if infant exhibits respiratory distress, temperature instability, or WBC is low (<5 x $10^9$/L), elevated (>30 x $10^9$/L, or left-shifted)
- symptoms may be non-specific
- CXR: hazy lung and/or distinct infiltrates (may be difficult to differentiate from RDS)
- neonates with pneumonia should be admitted to the neonatal ICU (NICU) with blood and CSF cultures and antibiotics for management

## Retinopathy of Prematurity

- see Ophthalmology, OP39

# Sepsis in the Neonate

**Table 34. Sepsis Considerations in the Neonate**

| Early Onset (<72 h) | Late Onset (72 h – 28 d) |
|---|---|
| Vertical transmission, 95% present within 24 h after birth<br>Risk factors:<br>Maternal infection: UTI, GBS positive, previous child with GBS, sepsis, or meningitis<br>Maternal fever/leukocytosis/chorioamnionitis<br>Prolonged rupture of membranes (>18 h)<br>Preterm labour<br>Pathogens: GBS, *E. coli*, *Listeria* are most common<br>Pneumonia more common with early onset sepsis | Acquired after birth<br>Most common in preterm infants in NICU (most commonly due to coagulase negative *Staphylococcus*)<br>Other pathogens implicated include GBS, anaerobes, *E. coli*, *Klebsiella* |

**Chronic Perinatal Infections**

**CHEAP TORCHES**
**C**hicken pox/shingles
**H**epatitis B
**E**pstein-Barr virus
**A**IDS (HIV)
**P**arvovirus B19 (erythema infectiosum)
**T**oxoplasmosis
**O**ther
**R**ubella virus
**C**ytomegalovirus/Coxsackievirus
**H**SV
**E**very STI
**S**yphilis

## Clinical Feature

- no reliable absolute indicator of occult bacteremia in infants <3 mo, most specific result has been WBC <5
- temperature instability (hypo/hyperthermia)
- respiratory distress, cyanosis, apnea
- tachycardia/bradycardia
- lethargy, irritability
- poor feeding, vomiting, abdominal distension, diarrhea
- hypotonia, seizures, lethargy
- jaundice, hepatomegaly, petechiae, purpura

## Investigations

- suspicion of neonatal sepsis requires "full septic workup"
  - CBC, blood and urine cultures, CXR, ± LP (CSF analysis: cell count, glucose, protein, culture, and PCR for viruses)
  - LP must be conducted if blood culture is positive due to increased risk of meningitis

## Management

- supportive care
- IV antibiotics: typically ampicillin + cefotaxime or ampicillin + gentamicin chosen as first-line empiric therapy
- choice of antibiotic and duration of treatment dependent on symptoms, culture results, maternal GBS status, local resistance patterns
- if meningitis suspected, consider IV ampicillin + cefotaxime ± vancomycin
- addition of IV acyclovir if HSV infection suspected

# Skin Conditions of the Neonate

**Table 35. Common Neonatal Skin Conditions**

| Neonatal Skin Condition | Description |
|---|---|
| **Vasomotor Response** (Cutis Marmorata, Acrocyanosis) | Transient mottling when exposed to cold; usually normal, particularly if premature |
| **Vernix Caseosa** | Soft, creamy, white layer covering baby at birth |
| **Congenital Dermal Melanocytosis** ('Mongolian Spots') | Slate grey macules over lower back and buttocks (may look like bruises); common in dark skinned infants |
| **Capillary Hemangioma** | Raised red lesion, which increases in size after birth and involutes; 50% resolved by 5 yr, 90% by 9 yr |
| **Erythema Toxicum** | Yellow-white papules/pustules surrounded by erythema, eosinophils within the lesions; common rash, resolves by 2 wk |
| **Milia** | Lesions 1-2 mm firm white pearly papules on nasal bridge, cheeks, and palate; self-resolving |
| **Transient Pustular Melanosis** | Brown macular base with pustules, seen more commonly in African American infants; may be present at birth |
| **Nevus Simplex** (Salmon Patch) | Transient macular vascular malformation of the eyelids and/or neck ("Angel Kiss" or "Stork Bite"); most lesions disappear by 1 yr of life |
| **Neonatal Acne** | Inflammatory papules and pustules mainly on face; self-resolving usually within 4 mo |

# Nephrology

## Common Pediatric Renal Diseases

**Table 36. Common Manifestations of Renal Disease**

| Neonate | Common Causes |
|---|---|
| Flank Mass | Hydronephrosis, polycystic disease (autosomal dominant or recessive subtypes), tumour |
| Hematuria | Renal vein thrombosis, asphyxia, malformation, trauma |
| Anuria/Oliguria | Bilateral renal agenesis, obstruction, asphyxia |
| **Child and Adolescent** | |
| Cola/Red-Coloured Urine | Acute GN (post-streptococcal, HSP, IgA nephropathy, etc.), hemoglobinuria (hemolysis), myoglobinuria (rhabdomyolysis) |
| Gross Hematuria | Urologic disease (nephrolithiasis, trauma, etc.), UTI, acute GN |
| Edema | Nephrotic syndrome, nephritis, acute/chronic renal failure, consider cardiac or liver disease |
| HTN | GN, renal failure, dysplasia (consider coarctation, drugs, endocrine causes) |
| Polyuria | DM, central and nephrogenic DI, renal Fanconi's syndrome (genetic/metabolic/acquired causes), hypercalcemia, polyuric renal failure (renal dysplasia) |
| Proteinuria | Orthostatic, nephrotic syndrome (MCD, etc.), GN |
| Oliguria | Dehydration, ATN, interstitial nephritis, acute or chronic kidney disease (i.e. renal failure) |
| Urgency | UTI, vulvovaginitis |

## Hemolytic Uremic Syndrome

### Definition
- simultaneous occurrence of the triad of:
  1. non-immune microangiopathic hemolytic anemia
  2. thrombocytopenia
  3. acute renal injury

### Epidemiology
- annual incidence of 1-2 per 100,000 in Canada
- most common cause of acute renal failure in children

### Etiology
- diarrhea positive HUS: 90% of pediatric HUS from *E. coli* O157:H7, shiga toxin, or verotoxin
- diarrhea negative HUS: other bacteria, viruses, drugs, familial/genetic

### Pathophysiology
- toxin binds, invades, and destroys colonic epithelial cells, causing bloody diarrhea
- toxin enters the systemic circulation, attaches to, and injures endothelial cells (especially in kidney), causing a release of endothelial products (e.g. von Willebrand factor, platelet aggregating factor)
- platelet/fibrin thrombi form in multiple organ systems (e.g. kidney, pancreas, brain, etc.) resulting in thrombocytopenia
- RBCs are forced through occluded vessels, resulting in fragmented RBCs (schistocytes) that are removed by the reticuloendothelial system (hemolytic anemia)

### Clinical Feature
- initial presentation of abdominal pain and diarrhea, followed by bloody diarrhea; within 5-7 d begins to show signs of anemia, thrombocytopenia, and renal insufficiency
- pallor, jaundice (hemolysis), edema, petechiae, HTN

### Investigations
- CBC (anemia, thrombocytopenia), blood smear (schistocytes), electrolytes, renal function, urinalysis (microscopic hematuria), stool cultures, and verotoxin/shigella toxin assay

### Management
- mainly supportive: nutrition, hydration, ventilation (if necessary), blood transfusion for symptomatic anemia
- monitor electrolytes and renal function: dialysis if electrolyte abnormality (hyperkalemia) cannot be corrected, fluid overload, or uremia
- steroids are not helpful
- antibiotics are contraindicated as death of bacteria leads to increased toxin release and worse clinical course

### Prognosis
- death in <5% of cases, 5-25% long-term renal damage (HTN, proteinuria, decreased renal function)

# Nephritic Syndrome

## Definition
- acute or chronic syndrome affecting the kidney, characterized by glomerular injury and inflammation
- defined by hematuria (>5 RBCs per high-powered microscope field), presence of dysmorphic RBCs, and RBC casts on urinalysis
- often accompanied by at least one of proteinuria (<50 mg/kg/d), edema, HTN, azotemia, and oliguria

## Epidemiology
- highest incidence in children aged 5-15 yr old

## Etiology
- humoral immune response to a variety of etiologic agents → immunoglobulin deposition → complement activation, leukocyte recruitment, release of growth factors/cytokines → glomerular inflammation and injury → porous podocytes → hematuria + RBC casts ± proteinuria
- HTN secondary to fluid retention and increased renin secretion by ischemic kidneys

**Table 37. Major Causes of Nephritic Syndrome**

| | Decreased C3 | Normal C3 |
|---|---|---|
| **Primary** (idiopathic) | Post-infectious GN (most common cause of acute GN in pediatrics)<br>Membranoproliferative<br>Type I (50-80%)<br>Type II (>80%) | IgA nephropathy<br>Idiopathic rapidly progressive GN<br>Anti-GBM disease |
| **Secondary** (systemic disease) | SLE<br>Bacterial endocarditis<br>Abscess or shunt nephritis<br>Cryoglobulinemia | HSP (very common)<br>Polyarteritis nodosa<br>Granulomatosis with polyangiitis<br>Goodpasture's syndrome |

**Nephritic Syndrome**

**PHAROH**
**P**roteinuria (<50 mg/kg/d)
**H**ematuria
**A**zotemia
**R**BC casts
**O**liguria
**H**TN

## Clinical Feature
- often asymptomatic; some overlap in clinical findings for nephritic and nephrotic syndrome
- gross hematuria, mild-moderate edema, oliguria, HTN
- signs and symptoms suggestive of underlying systemic causes (e.g. fever, arthralgias, rash, dyspnea, pulmonary hemorrhage)

## Investigations
- urine
  - dipstick (hematuria, 0 to 2+ proteinuria) and microscopy (>5 RBCs per high-powered microscope field, acanthocytes, RBC casts)
  - first morning urine protein/creatinine ratio (<200 mg/mmol)
- blood work
  - CBC, electrolytes, Cr, BUN, albumin
  - impaired renal function (↑ Cr and BUN) resulting in ↑ pH and electrolyte abnormalities (hyperkalemia, hyperphosphatemia, hypocalcemia)
  - mild anemia on CBC (secondary to hematuria)
  - hypoalbuminemia (secondary to proteinuria)
  - appropriate investigations to determine etiology: C3/C4 levels, serologic testing for recent streptococcal infection (ASOT, anti-hyaluronidase, anti-streptokinase, anti-NAD, anti-DNAse B), ANA, anti-DNA antibodies, ANCA, serum IgA levels, anti-GBM antibodies
- renal biopsy should be considered only in the presence of acute renal failure, no evidence of streptococcal infection, normal C3/C4

## Management
- treat underlying cause
- symptomatic
  - renal insufficiency: supportive (dialysis if necessary), proper hydration
  - HTN: salt and fluid restriction (but not at expense of renal function), ACEI or ARBs for chronic persistent HTN (not acute cases because ACEI or ARBs may decrease GFR further)
  - edema: salt and fluid restriction, possibly diuretics (avoid if significant intravascular depletion)
- corticosteroids if indicated: IgA nephropathy, lupus nephritis, etc.

## Prognosis
- dependent on underlying etiology
- complications include HTN, heart failure, pulmonary edema, chronic kidney injury (requiring renal transplant)

# Nephrotic Syndrome

## Definition
- clinical syndrome affecting the kidney, characterized by significant proteinuria, peripheral edema, hypoalbuminemia, and hyperlipidemia

## Epidemiology
- highest incidence in children 2-6 yr old, M>F

## Etiology
- primary (idiopathic): nephrotic syndrome in the absence of systemic disease (most common cause in pediatrics)
  - glomerular inflammation ABSENT on renal biopsy: MCD (85%), focal segmental glomerular sclerosis
  - glomerular inflammation PRESENT on renal biopsy: membranoproliferative GN, IgA nephropathy
- secondary: nephrotic syndrome associated with systemic disease or due to another process causing glomerular injury (<10% in pediatrics)
  - autoimmune: SLE, DM, rheumatoid arthritis
  - genetic: sickle cell disease, Alport syndrome
  - infections: hepatitis B/C, post-streptococcal, infective endocarditis, HUS, HIV
  - malignancies: leukemia, lymphoma
  - medications: captopril, penicillamine, NSAIDs, antiepileptics
  - vasculitides: HSP, granulomatosis with polyangiitis
- congenital: congenital nephropathy of the Finnish type, Denys-Drash syndrome, etc.

**PALE**
**P**roteinuria (>50 mg/kg/d)
Hypo**A**lbuminemia (<20 g/L)
Hyper**L**ipidemia
**E**dema

Daily protein excretion can be estimated from a random urine protein/creatinine ratio

## Clinical Feature
- non-specific symptoms such as irritability, malaise, fatigue, anorexia, or diarrhea
- edema
  - often first sign; detectable when fluid retention exceeds 3-5% of body weight
  - starts periorbital and often pretibial → edematous areas are white, soft, and pitting
  - gravity dependent: periorbital edema ↓ and pretibial edema ↑ over the day
  - anasarca may develop (i.e. marked periorbital and peripheral edema, ascites, pleural effusions, scrotal/labial edema)
- decrease in effective circulating volume (e.g. tachycardia, HTN, oliguria, etc.)
- foamy urine is a possible sign of proteinuria

## Investigations
- urine
  - urine dipstick (3 to 4+ proteinuria, microscopic hematuria) and microscopy (oval fat bodies, hyaline casts)
  - first morning urine protein/creatinine ratio (>200 mg/mmol)
- blood work
  - diagnostic: hypoalbuminemia (<25 g/L), hyperlipidemia/hypercholesterolemia (total cholesterol >5 mmol/L)
  - secondary: electrolytes (hypocalcemia, hyperkalemia, hyponatremia), renal function (↑ BUN and Cr), coagulation profile (↓ PTT)
  - appropriate investigations to rule out secondary causes: CBC, blood smear, C3/C4, ANA, hepatitis B/C titres, ASOT, HIV serology, etc.
- consider renal biopsy if: HTN, gross hematuria, ↓ renal function, low serum C3/C4, no response to steroids after 4 wk of therapy, frequent relapses (>2 in 6 mo), presentation before first yr of life (high likelihood of congenital nephrotic syndrome), presentation ≥12 yr (rule out more serious renal pathology than MCD)

## Management
- MCD: oral prednisone 2 mg/kg/d (or equivalent) for up to 12 wk → varicella status should be known before starting
- consider cytotoxic agents, immunomodulators, or high-dose pulse corticosteroid if steroid resistant
- symptomatic
  - edema: salt and fluid restriction, possibly diuretic (avoid if significant intravascular depletion); furosemide + albumin for anasarca
  - hyperlipidemia: generally resolves with remission; limit dietary fat intake; consider statin therapy if persistently nephrotic
  - hypoalbuminemia: IV albumin and furosemide not routinely given; consider if refractory edema
  - abnormal BP: control BP; fluid resuscitation if severe intravascular depletion; ACEI or ARBs for persistent HTN
- diet: no added salt; monitor caloric intake and supplement with $Ca^{2+}$ and Vit D if on corticosteroids
- daily weights and BP to assess therapeutic progress
- secondary infections: treat with appropriate antimicrobials; antibiotic prophylaxis not recommended; pneumococcal vaccine at diagnosis and varicella vaccine after remission; varicella Ig + acyclovir if exposed while on corticosteroids
- secondary hypercoagulability: mobilize, avoid hemoconcentration due to hypovolemia, prompt sepsis treatment; heparin if thrombi occur

**Side Effects of Long-Term Steroid Use**
- Increased appetite
- Weight gain
- Dorsal hump
- Impaired growth
- Behavioural changes
- Risk of infection
- Salt and water retention
- HTN
- Bone demineralization
- Skin striae

### Prognosis
- generally good: 80% of children responsive to corticosteroids
- up to 2/3 experience relapse, often multiple times; sustained remission with normal kidney function usually by adolescence
- complications: ↑ risk of infections (spontaneous peritonitis, cellulitis, sepsis); hypercoagulability due to decreased intravascular volume and antithrombin III depletion (PE, renal vein thrombosis); intravascular volume depletion, leading to hypotension, shock, renal failure; side effects of drugs

## Hypertension in Childhood

### Definition
- HTN: sBP and/or dBP ≥95th percentile for sex, age, and height on ≥3 occasions
- pre-HTN: sBP and/or dBP ≥90th percentile but <95th percentile or BP ≥120/80 irrespective of age, gender, and height

**Table 38. 95th Percentile Blood Pressures (mmHg)**

| | Female | | Male | |
|---|---|---|---|---|
| **Age (Yr)** | **50th Percentile for Height** | **75th Percentile for Height** | **50th Percentile for Height** | **75th Percentile for Height** |
| 1 | 104/58 | 105/59 | 103/56 | 104/57 |
| 6 | 111/74 | 113/74 | 114/74 | 115/75 |
| 12 | 123/80 | 124/81 | 123/81 | 125/82 |
| 17 | 129/84 | 130/85 | 136/87 | 138/87 |

Adapted from: the Fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. National Heart, Lung and Blood Institute. National Institutes of Health. May 2004

### Epidemiology
- prevalence: 3-5% for HTN, 7-10% for pre-HTN; M>F
- increasing prevalence of pre-HTN over the last 25+ yr

### Etiology
- primary HTN
  - diagnosis of exclusion
  - most common in older children (≥10 yr), especially if positive family history, overweight, and only mild HTN
  - responsible for ~90% of cases of HTN in adolescents, rarely in young children
- secondary HTN
  - identifiable cause of HTN (most likely etiology depends on age)
  - responsible for majority of childhood HTN
- always consider white coat HTN for all ages

**Table 39. Etiology of Secondary HTN by Age Group**

| System | Neonates | 1 mo-6 yr | 7-12 yr | >13 yr |
|---|---|---|---|---|
| **Endocrine/ Metabolic** | CAH | Wilms' tumour (↑ renin)<br>Neuroblastoma (↑ catecholamines) | Endocrinopathies* | Endocrinopathies* |
| **Renal** | Congenital renal disease | Renal parenchymal disease | Renal parenchymal disease | Renal parenchymal disease |
| **Vascular** | Coarctation of the aorta<br>Renal artery thrombosis | Coarctation of the aorta<br>RAS | Renovascular abnormalities | |
| **Drugs** | | Corticosteroids<br>Cyclosporine and tacrolimus | Corticosteroids<br>OCP<br>Cyclosporine and tacrolimus | Corticosteroids<br>OCP<br>Cyclosporine and tacrolimus<br>Recreational drugs (amphetamines, cocaine, etc.) |

*Note: may include hyperthyroidism, hyperparathyroidism, Cushing's syndrome, primary hyperaldosteronism/Conn's syndrome, pheochromocytoma

### Risk Factors
- primary HTN: male gender, positive family history, obesity, obstructive sleep apnea, African American, prematurity/LBW
- secondary HTN: history of renal disease, abdominal trauma, family history of autoimmune diseases, umbilical artery catheterization



**Signs of Secondary HTN**
- Edema (renal parenchymal disease)
- Abdominal or renal bruit (RAS)
- Differential 4 limb BP/diminished femoral pulses (coarctation)
- Abdominal mass (Wilms', neuroblastoma)
- Goitre/skin changes (hyperthyroidism)
- Ambiguous genitalia (CAH)

### Clinical Feature
- often asymptomatic, but can include FTT, fatigue, epistaxis
- symptoms of hypertensive emergency
  - neurologic: headache, seizures, focal complaints, change in mental status, visual disturbances
  - cardiovascular: symptoms of MI or heart failure (chest pain, palpitations, cough, SOB)
- symptoms of secondary HTN: guided by etiology; ask about medications and recreational drugs (current and past)
- physical exam: measure BP with correct cuff size, BMI, full neurologic exam, ophthalmoscopy, precordial exam, peripheral pulses, perfusion status

### Investigations
- laboratory
  - urine dipstick for hematuria and/or proteinuria (renal disease), urine catecholamines (pheochromocytoma, neuroblastoma)
  - blood work: renal function tests (electrolytes, Cr, BUN), consider renin and aldosterone levels (RAS, Conn's syndrome, Wilms' tumour)
  - other specific hormones if indicated on history and physical
- imaging: Echo (coarctation, heart function), abdominal U/S (RAS, abdominal mass), renal radionucleide imaging (renal scarring)

### Management
- treat underlying cause
- non-pharmacologic: modify concurrent cardiovascular risk factors (weight reduction, exercise, salt restriction, smoking cessation)
- pharmacologic: gradual lowering of BP using thiazide diuretics; no antihypertensives have been formally studied in children; if hypertensive emergencies use hydralazine, labetalol, sodium nitroprusside
- management of end-organ damage (e.g. retinopathy, LVH)
- consider referral to specialist

**Pediatric BP Calculation**
sBP= age x 2 + 90
dBP= 2/3 x sBP

### Prognosis
- end-organ damage (similar to adults) including LVH, CHF, cerebrovascular insults, renal disease, retinopathy

# Neurology

## Cerebral Palsy

### Definition
- a symptom complex, not a disease
- non-progressive central motor impairment syndrome due to insult to or anomaly of the immature CNS
- incidence: 1.5-2.5/1000 live births (industrialized nations)
- life expectancy is dependent on the degree of mobility and intellectual impairment, not on severity of CNS lesion

### Etiology
- often obscure, no definite etiology identified in 1/3 of cases
- 10% related to intrapartum asphyxia; 10% due to postnatal insult (infections, asphyxia, prematurity with IVH and trauma)
- association with LBW babies

### Clinical Feature
- general signs: delay in motor milestones, developmental delay, learning disabilities, visual/hearing impairment, seizures, microcephaly, uncoordinated swallow (aspiration)

**Table 40. Types of Cerebral Palsy**

| Type | % of Total | Characteristics | Area of Brain Involved |
|---|---|---|---|
| **Spastic** | 70-80% | Truncal hypotonia in first yr<br>Increased tone, increased reflexes, clonus<br>Can affect one limb (monoplegia), one side of body (hemiplegia), both legs (diplegia), or both arms and legs (quadriplegia) | UMN of pyramidal tract<br>Diplegia associated with periventricular leukomalacia in premature babies<br>Quadriplegia associated with HIE (asphyxia), higher incidence of intellectual disability |
| **Athetoid/ Dyskinetic** | 10-15% | Athetosis (involuntary writhing movements)<br>± chorea (involuntary jerky movements)<br>Can involve face, tongue (results in dysarthria) | Basal ganglia (may be associated with kernicterus) |
| **Ataxic** | <5% | Poor coordination, poor balance (wide based gait)<br>Can have intention tremor | Cerebellum |
| **Mixed** | 10-15% | More than one of the above motor patterns | |

### Investigations
- may include metabolic screen, chromosome studies, serology, neuroimaging (MRI), EMG, EEG (if seizures), ophthalmology assessment, audiology assessment

### Treatment
- maximize potential through multidisciplinary services such as primary care physician, OT, PT, SLP, school supports, etc.
- orthopedic management (e.g. dislocations, contractures, rhizotomy)
- management of symptoms: spasticity (baclofen, Botox®), constipation (stool softeners)

## Febrile Seizures

### Epidemiology
- most common cause of seizure in children (3-5% of children)
- M>F; age 6 mo-6 yr

### Clinical Feature
- often with associated illness or fever and family history
- no evidence of CNS infection/inflammation before or after seizure; no history of non-febrile seizures

**Table 41. Comparison of Typical and Atypical Febrile Seizures**

| **Simple/Typical** (70-80%) | **Complex/Atypical** (20-30%) |
|---|---|
| All of the following:<br>Duration <15 min (95% <5 min)<br>Generalized tonic-clonic<br>No recurrence in 24 h period<br>No neurological impairment or developmental delay before or after seizure | At least one of the following:<br>Duration >15 min<br>Focal onset or focal features during seizure<br>Recurrent seizures (>1 in 24 h period)<br>Previous neurological impairment or neurological deficit after seizure |

### Investigations
- history: determine focus of fever, description of seizure, medications, trauma history, development, family history
- physical exam: LOC, signs of meningitis, neurological exam, head circumference, focus of infection
- septic workup including LP if suspecting meningitis (strongly consider if child <12 mo; consider if child is 12-18 mo; only if meningeal signs present if child >18 mo)
- if typical febrile seizure, investigations only for determining focus of fever
- EEG/CT/MRI brain not warranted unless atypical febrile seizure or abnormal neurologic findings

### Management
- counsel and reassure patient and parents
  - febrile seizures do not cause brain damage
  - very small risk of developing epilepsy: 9% in child with multiple risk factors; 2% in child with typical febrile seizures compared to 1% in general population
  - 33% chance of recurrence (mostly within 1 yr of first seizure and in children <1 yr old)
- antipyretics and fluids for comfort (though neither prevent seizure)
- prophylaxis with antiepileptic drugs not recommended
- if high risk for recurrent or prolonged seizures, have rectal or sublingual lorazepam at home
- treat underlying cause of fever

## Hypotonia

- decreased resistance to passive movements – "floppy baby"

### Differential Diagnosis
- central: genetic (DS, Prader-Willi, Fragile X syndrome), metabolic (hypoglycemia, kernicterus), perinatal problems (asphyxia, ICH), endocrine (hypothyroidism, hypopituitarism), systemic illness (TORCH infection, sepsis, dehydration), CNS malformations, dysmorphic syndromes
- peripheral: motor neuron (spinal muscular atrophy, polio), peripheral nerve (Charcot-Marie-Tooth syndrome), neuromuscular junction (myasthenia gravis), muscle fibre (mitochondrial myopathy, muscular dystrophy, myotonic dystrophy)

### Clinical Feature
- proper assessment of tone requires accurate determination of GA
- differentiate between UMN and LMN lesion: spontaneous posture (spontaneous movement, movement against gravity, frog-leg position); muscle weakness; joint mobility (hyperextensibility); muscle bulk; presence of fasciculations



Causes of hypotonia that respond to rapid treatment: hypokalemia, hypermagnesemia, acidemia, toxins, drugs, hypoglycemia, seizure, infection, intracranial bleeding, hydrocephalus

- postural maneuvers
  - traction response: pull to sit, look for flexion of arms to counteract traction and head lag
  - axillary suspension: suspend infant by holding at axilla and lifting; hypotonic babies will slip through grasp because of low shoulder girdle tone
  - ventral suspension: infant is prone and supported under the abdomen by one hand; infant should be able to hold up extremities; inverted "U" posturing demonstrates hypotonia
- dysmorphic features, cognitive ability, reflexes, strength

### Investigations
- rule out systemic disorders (e.g. electrolytes, ABG, blood glucose, CK, and serum/urine investigations for multiple etiologies including mitochondrial causes)
- neuroimaging: MRI/MRA when indicated
- EMG, muscle biopsy/NCS
- chromosome analysis, genetic testing, metabolic testing, neuromuscular testing

### Management
- depends on etiology: some treatments available for specific diagnosis
- counsel parents on prognosis and genetic implications
- refer patients for specialized care, refer for rehabilitation, OT, PT, assess feeding ability

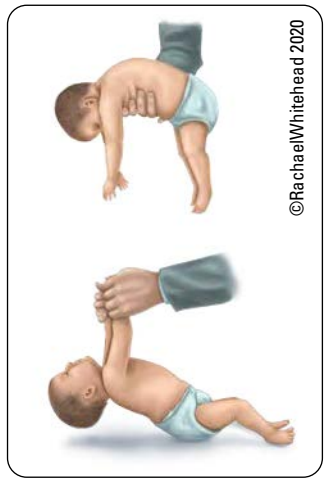



**Figure 17. Hypotonia**

## Neurocutaneous Syndromes

### Definition
- characterized by skin colour changes and tendency to form tumours of the CNS, PNS, viscera, and skin

In neurocutaneous syndromes, the younger the child at presentation, the more likely they are to develop intellectual disability

### NEUROFIBROMATOSIS TYPE I
- autosomal dominant but 50% are the result of new mutations
- also known as von Recklinghausen disease
- incidence 1:3000, mutation in NF1 gene on 17q11.2 (codes for neurofibromin protein)
- learning disorders, abnormal speech development, and seizures are common
- diagnosis of NF-1 requires 2 or more of:
  - ≥6 café-au-lait spots (>5 mm if prepubertal, >1.5 cm if postpubertal)
  - ≥2 neurofibromas of any type or one plexiform neurofibroma
  - ≥2 Lisch nodules (hamartomas of the iris)
  - optic glioma
  - freckling in the axillary or inguinal region
  - a distinctive bony lesion (e.g. sphenoid dysplasia, cortical thinning of long bones)
  - a first degree relative with confirmed NF-1
- management involves treatment of disease manifestations as they occur, as well as genetic counselling, OT, PT, and speech therapy as needed

### NEUROFIBROMATOSIS TYPE II
- autosomal dominant
- incidence 1:33,000
- characterized by predisposition to form intracranial, spinal tumours
- diagnosed when bilateral vestibular schwannomas are found, or a first-degree relative with NF-2 and either unilateral vestibular schwannoma, or any two of the following: meningioma, glioma, schwannoma, neurofibroma, posterior subcapsular lenticular opacities
- treatment consists of monitoring for tumour development and surgery

## Recurrent Headache

- see Neurology, N44

### Differential Diagnosis
- primary headache: tension, migraine, cluster
- secondary headache: see Neurology, N45

### General Assessment
- if unremarkable history and neurological and general physical exam is negative, most likely diagnosis is migraine or tension headache
- CT or MRI if history or physical reveals red flags
- inquire about level of disability, academic performance, after-school activities

**Headache – Red Flags**
- First and worst headache of their life
- Sudden onset
- Focal neurological deficits
- Constitutional symptoms
- Worse in morning
- Worse with bending over, coughing, straining
- Change in LOC
- Sudden mood changes
- Pain that wakes patient
- Fatigue
- Affecting school attendance

# Seizure Disorders

• see Neurology, N18

## Differential Diagnosis of Seizures in Children

- benign febrile seizure
- CNS: infection, tumour, HIE, trauma, hemorrhage
- metabolic: hypoglycemia, hypocalcemia, hyponatremia
- idiopathic epilepsy and epileptic syndromes
- others: neurocutaneous syndromes, AVM, drug ingestions/withdrawal
- seizure mimics



Heart problems, such as long QT syndrome and hypertrophic cardiomyopathy, are often misdiagnosed as epilepsy. Include cardiac causes of syncope in your differential diagnosis, particularly when the episodes occur during physical activity

## Investigations

- lab tests: CBC, electrolytes, calcium, magnesium, glucose
- toxicology screen if indicated
- EEG
- CT/MRI, if indicated (focal neurological deficit or has not returned to baseline several hours after seizure)
- consider LP if first-time non-febrile seizure (not indicated for determining recurrence risk of benign febrile seizures or to determine seizure type or epileptic syndrome)



**Seizure Mimics**

- Benign paroxysmal vertigo
- Breath holding
- Hypoglycemia
- Narcolepsy
- Night terror
- Pseudoseizure
- Syncope
- TIA
- Tic

## CHILDHOOD EPILEPSY SYNDROMES

### Infantile Spasms

- brief, repeated symmetric contractions of neck, trunk, extremities (flexion and extension) lasting 10-30 s
- occur in clusters; often associated with developmental delay; onset 4-8 mo
- 20% unknown etiology (usually good response to treatment); 80% due to metabolic or developmental abnormalities, encephalopathies, or are associated with neurocutaneous syndromes (usually poor response to treatment)
- can develop into West syndrome (infantile spasms, psychomotor developmental arrest, and hypsarrhythmia) or Lennox-Gastaut (see below)
- typical EEG: hypsarrhythmia (high voltage slow waves, spikes and polyspikes, background disorganization)
- management: ACTH, vigabatrin, benzodiazepines



**Ketogenic Diet and other Dietary Treatments for Epilepsy**
Cochrane DB Syst Rev 2012;3:CD001903
**Study:** Systematic review of all studies of ketogenic and related diets. Included the review of 4 RCTs, 6 prospective studies, and 5 retrospective studies.
**Population:** Adults and children with diagnosed epilepsy of any type.
**Intervention:** Ketogenic diet, control (placebo diet, any treatment with known antiepileptic properties).
**Main Outcome Measure:** Seizure control at 3, 6, 12 mo.
**Results:** Studies showed a response rate of at least 38-50% seizure reduction at 3 mo. This response was maintained for up to a year. A range of side effects were reported. The most frequent were gastrointestinal effects (30%).
**Conclusion:** The ketogenic diet is a valid option for people with medically-intractable epilepsy.

### Lennox-Gastaut

- characterized by triad of:
  1) multiple seizure types
  2) diffuse cognitive dysfunction
  3) slow generalized spike and slow wave EEG
- onset commonly 3-5 yr of age
- seen with underlying encephalopathy and brain malformations
- management: valproic acid, benzodiazepines, and ketogenic diet; however, response often poor

### Juvenile Myoclonic Epilepsy (Janz Syndrome)

- myoclonus particularly in morning; frequently presents as generalized tonic-clonic seizures
- adolescent onset (12-16 yr of age); autosomal dominant with variable penetrance
- typical EEG: 3.5-6 Hz irregular spike and wave, increased with photic stimulation
- management: lifelong treatment (valproic acid); excellent prognosis

### Childhood Absence Epilepsy

- multiple daily absence seizures lasting <30 s without post-ictal state that may resolve spontaneously or become generalized in adolescence
- peak age of onset 6-7 yr, F>M, strong genetic predisposition
- typical EEG: 3 Hz spike and wave
- management: valproic acid or ethosuximide

### Benign Focal Epilepsy of Childhood with Rolandic/Centrotemporal Spikes

- focal motor seizures involving tongue, mouth, face, upper extremity usually occuring in sleep-wake transition states; remains conscious, but aphasic post-ictally
- onset peaks at 5-10 yr of age; 16% of all non-febrile seizures; remits spontaneously in adolescence without sequelae
- typical EEG: repetitive spikes in centrotemporal area with normal background
- management: frequent seizures controlled by carbamazepine, no medication if infrequent seizures

### General Approach to Treatment

- education for patient and parents including education and precautions in daily life (e.g. buddy system, showers instead of baths)

- medication
  - initiate: treatment with drug appropriate to seizure type; often if >2 unprovoked afebrile seizures within 6-12 mo
  - optimize: start with one drug and increase dosage until seizures controlled
  - if no effect, switch over to another before adding a second antiepileptic drug
- continue antiepileptic drug therapy until patient free of seizures for >2 yr, then wean over 4-6 mo
- ketogenic diet (high fat diet): used in patients who do not respond to polytherapy or who do not wish to take medication (valproic acid contraindicated in conjunction with ketogenic diet because may increase hepatotoxicity)
- legal obligation to report to Ministry of Transportation if patient wishes to drive

### Generalized and Partial Seizures
- see Neurology, N18

# Respirology

## Asthma

### Definition
- see Respirology, R7
- inflammatory disorder of the airwarys characterized by recurrent episodes of reversible small airway obstruction, resulting from airway hyperresponsiveness to endogenous and exogenous stimuli
- very common, presents most often in early childhood
- associated with other atopic diseases such as allergic rhinitis or atopic dermatitis

### Clinical Feature
- episodic bouts of wheezing, dyspnea, tachypnea, cough (usually at night/early morning, with activity, or cold exposure)
- physical exam may reveal hyper-resonant chest, prolonged expiration, wheeze
- symptoms may be exacerbated by "triggers": URTI (viral or *Mycoplasma*), weather (cold exposure, humidity changes), allergens (pets), irritants (cigarette smoke), exercise, emotional stress, drugs (ASA, β-blockers)

### Classification
- mild: occasional attacks of wheezing or coughing (<2/wk); symptoms respond quickly to inhaled bronchodilator; never needs systemic corticosteroids
- moderate: more frequent episodes with symptoms persisting and chronic cough; decreased exercise tolerance; sometimes needs systemic corticosteroids
- severe: daily and nocturnal symptoms; frequent ED visits and hospitalizations; usually needs systemic corticosteroids

### Management
- acute
  - $O_2$ (keep $O_2$ saturation >94%) and fluids if dehydrated
  - β2-agonists: salbutamol (Ventolin®) MDI + spacer (nebulized or IV in very severe episodes with impending respiratory failure), 5 puffs (<20 kg) or 10 puffs q20min for first h (>20 kg)
  - ipratropium bromide (Atrovent®) if severe: MDI + spacer, 3 puffs (<20 kg) or 6 puffs (>20 kg) q20min with salbutamol, or add to first 3 salbutamol masks (0.25 mg if <20 kg, 0.5mg if >20 kg)
  - steroids: prednisone (1-2 mg/kg x 5 d) or dexamethasone (0.3 mg/kg/d x 5 d or 0.6 mg/kg/d x 2 d); in severe disease, use IV steroids
  - if no response, add magnesium sulphate
  - continue to observe; can discharge patient if asymptomatic for 2-4 h after last dose
- chronic
  - education, emotional support, avoid allergens or irritants, develop an "action plan"
  - exercise program (e.g. swimming)
  - monitor respiratory function with peak flow metre (improves self-awareness of status)
  - PFTs for children >6 yr
  - reliever therapy: short acting β2-agonists (e.g. salbutamol)
  - controller therapy (first line therapy for all children): low dose daily inhaled corticosteroids
  - second line therapy for children <12 yr: moderate dose of daily inhaled corticosteoroids
  - second line therapy for children >12 yr: leukotriene receptor antagonist OR long acting β2-agonist in conjunction with low dose inhaled corticosteroids; leukotriene receptor antagonist monotherapy may be considered an alternative second line therapy
  - severe asthma unresponsive to first and second line treatments: injection immunotherapy
  - aerochamber for children using daily inhaled corticosteroids
- indications for hospitalization
  - ongoing need for supplemental $O_2$
  - persistently increased work of breathing
  - β2-agonists are needed more often than q4h after 4-8 h of conventional treatment
  - patient deteriorates while on systemic steroids

**Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection**
Pediatrics 2014 Aug;134(2):415-20
Palivizumab prophylaxis is recommended for the first year of life for infants born before 29 wk gestation, and preterm infants with chronic lung disease of maturity (born at <32 wk gestation and requiring >21% oxygen for at least 28 d after birth). Such prophylaxis may be administered in the first yr of life to infants with hemodynamically significant heart disease, and a maximum of 5 monthly 15 mg/kg doses may be administered during the RSV season to infants requiring it; infants born during the RSV season may need fewer doses. Prophylaxis may be considered in the first yr of life for children with pulmonary abnormalities or neuromuscular disease impairing the ability to clear secretions from the upper airway, and may be considered for children younger than 24 mo who are profoundly immunocompromised during the RSV season. Palivizumab prophylaxis is only recommended in the second year of life for children who required at least 28 d of supplemental oxygen after birth with ongoing medical intervention needs. Monthly prophylaxis should be discontinued in children experiencing breakthrough RSV hospitalizations. Insufficient evidence exists to support the use of prophylaxis for children with cystic fibrosis or Down's syndrome.

**Canadian Pediatric Asthma Consensus Guidelines for Assessing Adequate Control of Asthma**
CMAJ 2005;173(6 Suppl):S12-14
- Daytime symptoms <4 d/wk
- Night time symptoms <1 night/wk
- Normal physical activity
- Mild and infrequent exacerbations
- No work/school absenteeism
- Need for β-agonist <4 doses/wk
- $FEV_1$ or peak expiratory flow ≥90% of personal best
- Peak expiratory flow diurnal variation <10-15%

# Bronchiolitis

### Definition
- LRTI, usually in children <2 yr, that has wheezing and signs of respiratory distress

### Epidemiology
- the most common LRTI in infants, affects 50% of children in first 2 yr of life; peak incidence at 6 mo, winter or early spring
- increased incidence of asthma in later life

### Etiology
- RSV (>50%), parainfluenza, influenza, rhinovirus, adenovirus, *M. pneumoniae* (rare)

### Clinical Feature
- prodrome of URTI with cough and/or rhinorrhea, possible fever
- feeding difficulties, irritability
- wheezing, crackles, respiratory distress, tachypnea, tachycardia, retractions, poor air entry; symptoms often peak at 3-4 d

### Investigations
- routine investigations are not required when bronchiolitis is suspected (Choosing Wisely)
- CXR (only in poor response to therapy or atypical disease): air trapping, peribronchial thickening, atelectasis, increased linear markings

### Management
- self-limiting disease with peak symptoms usually lasting 2-3 wk
- mild to moderate distress
  - supportive: PO or IV hydration, antipyretics for fever, regular or humidified high flow $O_2$
- severe distress
  - as above ± intubation and ventilation as needed
  - consider rebetol (Ribavirin®) in high risk groups: bronchopulmonary dysplasia, CHD, congenital lung disease, immunodeficient
- monthly RSV-Ig or palivizumab (monoclonal antibody against the F-glycoprotein of RSV) is protective against severe disease in high risk groups; case fatality rate <1%
- bronchodilators, corticosteroids and antibiotics have no therapeutic value (unless there is secondary bacterial pneumonia)
- indications for hospitalization
  - hypoxia: $O_2$ saturation <92% on initial presentation
  - persistent resting tachypnea >60/min and retractions after several salbutamol masks
  - past history of chronic lung disease, hemodynamically significant cardiac disease, neuromuscular problem, immunocompromised
  - young infants <6 mo old (unless extremely mild)
  - significant feeding problems
  - social problem (e.g. inadequate care at home)

**Bronchodilators for Bronchiolitis**
Cochrane DB Syst Rev 2010;12:CD001266
**Purpose**: To assess the effects of bronchodilators in infants with acute bronchiolitis.
**Methods**: Meta-analysis of placebo-controlled RCTs evaluating bronchodilators for bronchiolitis. Oxygen saturation was the main outcome.
**Results**: 30 trials with 1992 infants with bronchiolitis were included. Oxygen saturation did not improve with bronchodilators (mean difference (MD) -0.43, 95% CI -0.92 to 0.06). Neither outpatient (11.9% vs. 15.9%, OR 0.75, 95% CI 1.21) nor inpatient (MD 0.06, 95% CI -0.27 to 0.39) reduced hospitalization rates. Effects on oximetry seen in inpatients (MD -0.62, 95% CI -1.40 to 0.16) were slightly larger than for outpatients (MD -0.25, 95% CI -0.61 to 0.11). No change in average clinical score was seen in inpatients (standardized MD -0.14, 95% CI -0.41 to 0.12), while a statistically significant decrease was seen in outpatients (MD -0.42, 95% CI -0.79 to -0.06). Adverse events included tachycardia, oxygen desaturation, and tremors.
**Results**: Bronchodilators do not improve oxygen saturation, rates of hospital admission, duration of hospitalizations, or durations to resolution of illness. They are not considered effective in routine management of bronchiolitis, especially given their adverse effects.

Children with bronchiolitis do not respond to ipratropium bromide (Atrovent®) or steroids

# Choanal Atresia

- **definition**: obliteration or blockage of the posterior nasal aperture, associated with bony abnormalities of the pterygoid plates and midfacial growth abnormalities
- **epidemiology**: 1/7000 live births
  - associated with bony abnormalities of the pterygoid plates and midfacial growth abnormalities
- **diagnosis**: by CT with intranasal contrast
- **treatment**: depends on extent
  - immediate treatment of bilateral choanal atresia: placement of an oral airway and initiation of gavage feedings
  - long term treatment: surgery

# Cystic Fibrosis

- see Respirology, R12

### Etiology
- 1 per 3000 live births, mostly Caucasians
- autosomal recessive, CFTR gene found on chromosome 7 (ΔF508 mutation in 70%, but >1600 different mutations identified) resulting in a dysfunctional chloride channel on the apical membrane of cells
- leads to relative dehydration of airway secretions, resulting in impaired mucociliary transport and airway obstruction

### Clinical Feature
- neonatal: meconium ileus, prolonged jaundice, antenatal bowel perforation
- infancy: pancreatic insufficiency with steatorrhea and FTT (despite voracious appetite), anemia, hypoproteinemia, hyponatremia

**CF Presenting Signs**

**CF PANCREAS**
**C**hronic cough and wheezing
**F**TT
**P**ancreatic insufficiency (symptoms of malabsorption such as steatorrhea)
**A**lkalosis and hypotonic dehydration
**N**eonatal intestinal obstruction (meconium ileus)/Nasal polyps
**C**lubbing of fingers/Chest radiograph with characteristic changes
**R**ectal prolapse
**E**lectrolyte elevation in sweat, salty skin
**A**bsence or congenital atresia of vas deferens
**S**putum with *S. aureus* or *P. aeruginosa* (mucoid)
- Pancreatic dysfunction – determined by 3 d fecal fat collection
- Genetics – useful where sweat chloride test is equivocal

- childhood: heat intolerance, wheezing or chronic cough, recurrent chest infections (*S. aureus, P. aeruginosa, H. influenzae*), hemoptysis, nasal polyps, distal intestinal obstruction syndrome, rectal prolapse, clubbing of fingers
- older patients: COPD, infertility (males), decreased fertility (female)

### Investigations
- sweat chloride test x 2 (>60 mEq/L)
  - false positive tests: malnutrition, atopic dermatitis, hypothyroidism, hypoparathyroidism, GSD, adrenal insufficiency, G6PD, Klinefelter syndrome, technical issues, autonomic dysfunction, familial cholestasis syndrome
  - false negative tests: technical problem with test, malnutrition, skin edema, mineralocorticoids
- CFTR gene mutation analysis
- disease often detected during newborn genetic screening; positive result requires DNA testing and subsequent sweat choride testing

### Management
- nutritional counselling: high calorie diet, pancreatic enzyme replacements, fat soluble vitamin supplements
- management of chest disease: physiotherapy, postural drainage, exercise, bronchodilators, aerosolized DNAase and inhaled hypertonic saline, antibiotics (e.g. cephalosporin, cloxacillin, ciprofloxacin, inhaled tobramycin depending on sputum C&S), lung transplantation
- genetic counselling

### Complications
- respiratory failure, pneumothorax (poor prognostic sign), cor pulmonale (late), pancreatic fibrosis with DM, gallstones, cirrhosis with portal HTN, infertility (male)
- early death (current median survival in Canada is 46.6 yr)

## Dyspnea

### Approach to Dyspnea
- determine if patient is sick or not sick; ABCs
- history: onset, previous episodes, precipitating events, associated symptoms, past medical/family history of respiratory disease
- physical exam: vitals, $SpO_2$, evidence of cyanosis, respiratory, cardiovascular
- investigations: CBC and differential, electrolytes, BUN, Cr, NP swab, ABG, CXR, ECG (based on clinical findings)

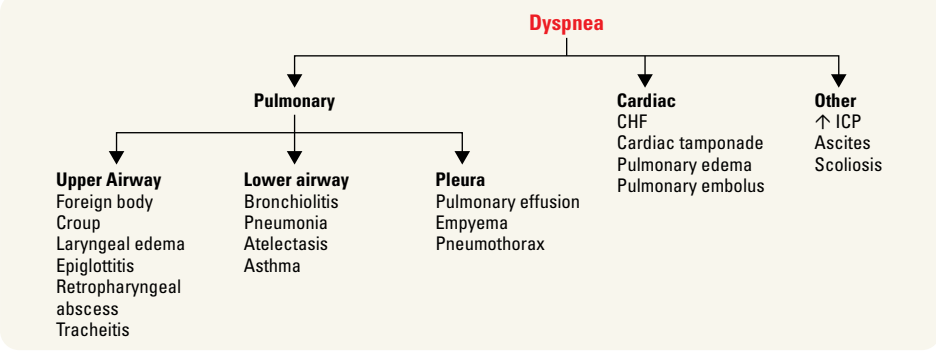



**Figure 18. Approach to dyspnea in childhood**

## Pneumonia

### Etiology
- inflammation of pulmonary tissue, associated with consolidation of alveolar spaces

### Clinical Feature
- incidence is greatest in first year of life with viral causes being most common in children <5 yr
- fever, cough, tachypnea
- CXR: diffuse, streaky infiltrates bilaterally
- bacterial causes may present with cough, fever, chills, dyspnea, more dramatic CXR changes (e.g. lobar consolidation, pleural effusion)

### Management
- supportive therapy: hydration, antipyretics, humidified $O_2$

**Table 42. Common Causes and Treatment of Pneumonia at Different Ages**

| Age | Bacterial | Viral | Atypical Bacteria | Treatment |
|---|---|---|---|---|
| **Neonates** | GBS<br>*E. coli*<br>*Listeria* | CMV<br>Herpes virus<br>Enterovirus | *Mycoplasma hominis*<br>*Ureaplasma urealyticum* | Ampicillin + gentamicin / tobramycin (add erythromycin if suspect *Chlamydia*) |
| **1-3 mo** | *S. aureus*<br>*H. influenzae*<br>*S. pneumoniae*<br>*B. pertussis* | CMV, RSV<br>Influenza<br>Parainfluenza | *Chlamydia trachomatis*<br>*Ureaplasma urealyticum* | Cefuroxime OR ampicillin ± erythromycin OR clarithromycin |
| **3 mo-5 yr** | *S. pneumoniae*<br>*S. aureus*<br>*H. influenzae*<br>GAS | RSV<br>Adenovirus<br>Influenza | *Mycoplasma pneumoniae*<br>TB | Amoxicillin (if mild) OR ampicillin OR cefuroxime |
| **>5 yr** | *S. pneumoniae*<br>*H. influenzae*<br>*S. aureus* | Influenza<br>Varicella<br>Adenovirus | *Mycoplasma pneumoniae*<br>*Chlamydia pneumoniae*<br>TB<br>*Legionella pneumophila* | Erythromycin OR clarithromycin (1st line) OR ampicillin OR cefuroxime |

# Respiratory Tract Diseases

## LOWER RESPIRATORY TRACT DISEASE

- obstruction of airways below thoracic inlet, produces more expiratory sounds
- classic symptom: wheezing

### Differential Diagnosis of Wheezing

- common: asthma (recurrent wheezing episodes, identifiable triggers, typically over 6 yr), bronchiolitis (first episode of wheezing, usually under 1 yr), recurrent aspiration (often neurological impairment), pneumonia (fever, cough, malaise)
- uncommon: foreign body (acute unilateral wheezing and coughing), CF (prolonged wheezing, unresponsive to therapy), bronchopulmonary dysplasia (often develops after prolonged ventilation in the newborn)
- rare: CHF, mediastinal mass, bronchiolitis obliterans, tracheobronchial anomalies

## UPPER RESPIRATORY TRACT DISEASE

- diseases above the thoracic inlet characterized by inspiratory stridor, hoarseness, and suprasternal retractions
- differential diagnosis of stridor: croup, bacterial tracheitis, epiglottitis, foreign body aspiration, subglottic stenosis (congenital or iatrogenic), laryngomalacia/tracheomalacia (collapse of airway cartilage on inspiration), retropharyngeal abscess

**Table 43. Common Upper Respiratory Tract Infections in Children**

| | Croup (Laryngotracheobronchitis) | Bacterial Tracheitis | Epiglottitis |
|---|---|---|---|
| **Anatomy** | Subglottic laryngitis | Subglottic tracheitis | Supraglottic laryngitis |
| **Epidemiology** | Common in children <6 yr, with peak incidence between 7-36 mo<br>Common in fall and early winter | Rare<br>All age groups | Very rare – due to Hib vaccination<br>Usually older (2-6 yr) |
| **Etiology** | Parainfluenza (75%)<br>Influenza A and B<br>RSV<br>Adenovirus | *S. aureus*<br>*H. influenzae*<br>α-hemolytic strep<br>Pneumococcus<br>*M. catarrhalis* | *H. influenzae*<br>β-hemolytic strep |
| **Clinical Presentation** | Common prodrome: rhinorrhea, pharyngitis, cough ± low-grade fever<br>Hoarse voice<br>Barking cough<br>Stridor<br>Worse at night | Similar symptoms as croup, but more rapid deterioration with high fever<br>Toxic appearance<br>Does not respond to croup treatments | Toxic appearance<br>Rapid progression<br>4 **D**s – **d**rooling, **d**ysphagia, **d**ysphonia, **d**istress<br>Stridor<br>Tripod position<br>Sternal recession<br>Anxious<br>Fever (>39°C) |
| **Investigations** | Clinical diagnosis<br>CXR in atypical presentation: "steeple sign" from subglottic narrowing | Clinical diagnosis<br>Endoscopy: definitive diagnosis | Clinical diagnosis<br>Avoid examining the throat to prevent further respiratory exacerbation |
| **Treatment** | Stridor at rest is an EMERGENCY<br>No evidence for humidified $O_2$<br>Dexamethasone: PO 1 dose<br>Racemic epinephrine: nebulized, 1-3 doses, q1-2h<br>Intubation if unresponsive to treatment | Usually requires intubation<br>IV antibiotics | Intubation<br>Antibiotics<br>Prevented with Hib vaccine |



**Croup**
Stridor at rest is an emergency

# Rheumatology

## Growing Pains

### Epidemiology
- age 2-12 yr, M=F

### Clinical Feature
- diagnosis of exclusion
- intermittent, non-articular pain in childhood with normal physical exam findings
- pain at night, often bilateral and limited to the calf, shin, or thigh; typically short-lived
- relieved by heat, massage, mild analgesics
- child is well, asymptomatic during the day, no functional limitation
- possible family history of growing pains

### Management
- lab investigations not necessary if typical presentation; reassurance and supportive management

## Juvenile Idiopathic Arthritis

- a heterogenous group of conditions characterized by persistent arthritis in children <16 yr
- diagnosis: arthritis in ≥1 joint(s); duration ≥6 wk; onset age <16 yr old; exclusion of other causes of arthritis; classification defined by features/number of joints affected in the first 6 mo of onset

### Systemic Arthritis (Still's Disease)
- onset at any age, M=F
- once or twice daily fever spikes (>38.5°C) ≥2 d/wk with temperature returning below baseline; children usually acutely unwell during fever episodes
- extra-articular features: erythematous "salmon-coloured" maculopapular rash, lymphadenopathy, hepatosplenomegaly, leukocytosis, thrombocytosis, anemia, serositis
- arthritis may occur weeks to months later
- high ESR, CRP, WBC, platelet count

### Oligoarticular Arthritis (1-4 joints)
- most common type of JIA
  - onset early childhood (<5 years of age), F>M
- persistent: affects no more than 4 joints during the disease course
- extended: affects more than 4 joints after the first 6 mo
- typically affects large joints: knee most common, elbows, wrists; hip involvement unusual
- ANA positive ~60-80%, RF negative
- screening eye exams for asymptomatic anterior uveitis (occurs in ~30%)
- complications: knee flexion contracture, quadriceps atrophy, leg-length discrepancy, growth disturbances, uveitis

### Polyarticular Arthritis (5 or more joints)
- ANA positive in 50%, uveitis in 10%
- RF negative (usually negative)
  - onset: 2-4 yr and 6-12 yr, F>M
  - symmetrical involvement of large and small joints of hands and feet, TMJ, cervical spine
- RF positive
  - onset: late childhood/early adolescence, F>M
  - similar to the aggressive form of adult rheumatoid arthritis
  - severe, rapidly destructive, symmetrical arthritis of large and small joints
  - may have rheumatoid nodules at pressure points (elbows, knees)
  - unremitting disease, persists into adulthood

### Enthesitis-Related Arthritis
- onset: late childhood/adolescence, M>F
- arthritis and/or enthesitis (inflammation at the site where tendons or ligaments attach to the bone)
- weight bearing joints, especially hip and intertarsal joints
- risk of developing ankylosing spondylitis in adulthood
- asymmetric involvement of lower limb joints, associated with HLA-B27 and development of symptomatic uveitis/ iritis

### Psoriatic Arthritis
- onset: 2-4 yr and 9-11 yr, F>M
- arthritis and psoriasis OR arthritis and at least two of:
  - dactylitis, nail pitting or other abnormalities, or family history of psoriasis in a 1st degree relative
  - asymmetric or symmetric small or large joint involvement
- erythematous, scaly lesions on scalp, post-auricular area, peri-umbilicus or over extensor surfaces of elbows and knees

### Management
- goals of therapy: eliminate inflammation, prevent joint damage, promote normal growth and development as well as normal function, minimize medication toxicity
- exercise (moderate, fitness, flexibility and strengthening exercises) to maintain ROM and muscle strength
- multidisciplinary approach: OT/PT, social work, orthopedics, ophthalmology, rheumatology
- 1st line drug therapy: NSAIDs, intra-articular corticosteroids
- 2nd line drug therapy: DMARDs (methotrexate, sulfasalazine, leflunamide), corticosteroids (acute management of severe arthritis, systemic symptoms of JIA, topical eye drops for uveitis), biologic agents (IL1, IL6 inhibition for systemic arthritis, TNF antagonist for polyarticular JIA)

# Limb Pain

## Evaulation of Limb Pain

**Table 44. Differential Diagnosis of Limb Pain**

| Cause | <3 yr | 3-10 yr | >10 yr |
|---|---|---|---|
| **Trauma** | x | x | x |
| **Infectious** | | | |
| Septic arthritis | x | x | x |
| Osteomyelitis | x | x | x |
| **Inflammatory** | | | |
| Transient synovitis | x | x | |
| JIA | x | x | x |
| Spondyloarthritis | | x | x |
| SLE | | x | x |
| Dermatomyositis | | x | x |
| HSP | | x | x |
| **Anatomic/Orthopedic** | | | |
| Legg-Calvé-Perthes disease | | x | x |
| Slipped capital femoral epiphysis | | | x |
| Osgood-Schlatter disease | | | x |
| **Neoplastic** | | | |
| Leukemia | x | x | x |
| Neuroblastoma | x | x | x |
| Bone tumour | | x | x |
| **Hematologic** | | | |
| Hemophilia (hemarthrosis) | x | x | x |
| Sickle cell anemia | x | x | x |
| **Pain Syndromes** | | | |
| Growing pains | | x | x |
| Fibromyalgia | | x | x |
| Complex regional pain syndrome | | | x |

- must rule out infection, malignancy, and acute orthopedic conditions

### Clinical Feature
- demographics (age, gender)
- pattern of onset and progression of symptoms (including acuity and chronicity)
- morning stiffness, limp/weight-bearing status, night pain
- joint involvement (type, distribution) ± spine (axial) involvement
- extra-articular manifestations and systemic symptoms
- functional status – activities of daily living
- family history (arthritis, IBD, psoriasis, spondyloarthropathies, uveitis, bleeding disorders, sickle cell anemia)
- past medical illness, intercurrent infection, travel, sick contact history, joint injury

### Physical Exam
- growth parameters
- screening examination (pediatric gait, arms, legs, spine exam)
- joint exam: inspection/palpation (swelling, erythema, warmth, tenderness, deformity), ROM
- adjacent structures (bone, tendon, muscle, skin)
- leg length
- neurologic exam

### Investigations
- basic: CBC and differential, blood smear, ESR, CRP, x-ray
- as indicated: blood (ANA, RF, culture, viral/bacterial serology, CK, PTT, sickle cell screen, immunoglobulins, complement), urinalysis, synovial fluid (cell count, Gram stain, culture), TB skin test, imaging, bone marrow aspiration, slit lamp exam



**Red Flags for Limb Pain**
- Fever
- Pinpoint pain/tenderness
- Pain out of proportion to degree of inflammation
- Night pain
- Weight loss
- Erythema
- Unexplained fractures

# Lyme Arthritis

- see Infectious Diseases, ID20
- caused by spirochete *Borrelia burgdorferi*
- incidence highest among 5-10 yr olds
- do not treat children <8 yr old with doxycycline (may cause permanent tooth discolouration)

# Reactive Arthritis

- see Rheumatology, RH24
- arthritis (typically the knee) follows bacterial infection, especially with *Salmonella, Shigella, Yersinia, Campylobacter, Chlamydia,* and most commonly *Streptococcus* (post-streptococcal reactive arthritis)
- typically resolves spontaneously
- may progress to chronic illness or Reiter's syndrome (urethritis, conjunctivitis)

# Septic Arthritis and Osteomyelitis

- **MEDICAL EMERGENCY**: prompt intravenous antibiotics, followed by 4-6 weeks of oral antibiotics
- see Orthopedic Surgery, OR10

**Table 45. Microorganisms and Treatment Involved in Septic Arthritis/Osteomyelitis**

| Age | Pathogens | Treatment |
|---|---|---|
| Neonate | GBS, *S. aureus,* Gram negative bacilli | Cloxacillin + gentamicin OR cloxacillin + cefotaxime |
| Infant (1-3 mo) | *Strep.* spp., *Staph.* spp., *H. influenzae* Pathogens as per neonate | Cloxacillin + cefotaxime OR cefuroxime |
| Child | *S. aureus, S. pneumoniae,* GAS | Cefazolin OR cloxacillin OR clindamycin |
| Adolescent | As above; also *N. gonorrhoeae* | Ceftriaxone OR cefixime + azithromycin |

GAS = group A *Strep*; GBS = group B *Strep* Adapted from Tse SML, Laxer RM. Pediatrics in Review 2006;27:170-179

# Systemic Lupus Erythematosus

- see Rheumatology, RH11
- autoimmune illness affecting multiple organ systems
- incidence 1/1000, more commonly age >10, F:M = 10:1
- childhood-onset SLE vs. adult-onset SLE: children have more active disease, are more likely to have renal disease, and children receive more intensive drug therapy and have a poorer prognosis

# Transient Synovitis of the Hip

- benign, self-limited inflammatory joint disorder, usually occurs after URTI, pharyngitis, AOM
- key is to differentiate from septic arthritis

## Epidemiology

- age 3-10 yr, M>F, more common on right side

## Clinical Feature

- afebrile or low-grade fever, pain typically occurs in hips, knees (referred from hip); painful limp but full ROM (pain not as pronounced as in joint or bone infections), child does not look "toxic"
  - pain is not disabling and gradually worsens over few days, can have sudden onset of symptoms
- symptoms resolve over 7-10 d

## Investigations

- WBC within normal limits; ESR and CRP may be mildly elevated
- joint effusions may be seen on ultrasound
  - aspirate joint and examine synovial fluid if suspicious for septic arthritis
  - MRI if suspicious for osteomyelitis or periarticular pyomyositis
- diagnosis of exclusion

## Treatment

- symptomatic and anti-inflammatory medications
  - usually resolves with 24-48 h

## Complications

- Legg-Calve-Perthes Disease

# Vasculitides

## HENOCH-SCHÖNLEIN PURPURA

- most common vasculitis of childhood, peak incidence 4-10 yr, M:F = 2:1
- vasculitis of small vessels
- often have history of URTI 1-3 wk before onset of symptoms

### Clinical Feature

- clinical triad: 1) palpable purpura, 2) abdominal pain, 3) arthritis
- skin: palpable, non-thrombocytopenic purpura in lower extremities and buttocks, edema, scrotal swelling
- joints: arthritis/arthralgia involving large joints associated with painful edema
- GI: abdominal pain, GI bleeding, intussusception
- renal: microscopic hematuria, IgA nephropathy, proteinuria, HTN, renal failure in <5%

### Investigation

- no routine investigations performed – diagnosis is mainly based on clinical features
- urinalysis (blood, protein creatinine ratio), serum (urea/electrolytes, creatinine, albumin, elevated IgA)
- skin/renal biopsy – IgA deposition
- ultrasound – interssusception/perforation, testicular pain/swelling
- rule out other autoimmune conditions/vasculitides

### Management

- mainly supportive (e.g. elevation for edema)
- anti-inflammatory medications for joint pain, corticosteroids for select patients
- monitor for protein on urinalysis and hypertension every month for 6 mo, checking for renal disease, which may develop late (immunosuppressive therapy if severe)

### Prognosis

- self-limited, resolves within 4 wk
- recurrence in about one-third of patients
- long-term prognosis dependent on severity of nephritis

## KAWASAKI DISEASE

- acute vasculitis of unknown etiology (likely triggered by infection)
- medium-sized vasculitis with predilection for coronary arteries
- most common cause of acquired heart disease in children in developed countries
- peak age: 3 mo-5 yr; Asians > Blacks > Caucasians



**Kawasaki Diagnostic Criteria: "CREAM"**
**C**onjunctival injection
**R**ash
**E**dema of hands and feet
**A**denopathy
**M**ucosal changes

### Diagnostic Criteria

- fever persisting ≥5 d AND ≥4 of the following features
  1. bilateral, non-exudative conjunctival injection
  2. oral mucous membrane changes (fissured lips, strawberry tongue, injected pharynx)
  3. changes of the peripheral extremities
     - acute phase: extremity changes including edema of hands and feet or erythema of palms or soles
     - subacute phase: periungual desquamation
  4. polymorphous rash
  5. cervical lymphadenopathy >1.5 cm in diameter (usually unilateral)
- exclusion of other diseases (e.g. scarlet fever, measles)
- atypical Kawasaki disease: fever persisting ≥5 d and 2-3 of the above criteria
  - further evaluation dictated by CRP, ESR, and supplemental laboratory criteria

### Management

- initial therapy: IVIG (2g/kg) and low (anti-inflammatory) dose of ASA (3-5 mg/kg/d)
- once afebrile >48 h: low (anti-platelet) dose of ASA until platelets normalize, or longer if coronary artery involvement
- IVIg within 10 d of onset reduces risk of coronary aneurysm formation
- baseline 2D-Echo and follow-up periodic 2D-Echo (usually at 2, 6 wk)

### Complications

- coronary artery vasculitis with aneurysm formation occurs in 20-25% of untreated children, <5% if receive IVIg within 10 d of fever
- 50% of aneurysms regress within 2 yr
- anticoagulation for multiple or large coronary aneurysms
- risk factors for coronary disease: male, age <1 or >9 yr, fever >10 d, Asian or Hispanic ethnicity, thrombocytopenia, hyponatremia

# Common Medications

**Table 46. Commonly Used Medications in Pediatrics**

| Drug Name | Dosing Schedule | Indications | Comments |
|---|---|---|---|
| acetaminophen | 10-15 mg/kg/dose PO q4-6h prn | Analgesic, antipyretic | Not to exceed 60 mg/kg/d in neonates or 75 mg/kg/d in older children to a max of 4 g/d<br>Causes hepatotoxicity at high doses |
| amoxicillin | 80-90 mg/kg/d PO divided q8h | Otitis media | |
| dexamethasone | 0.6 mg/kg PO x 1<br>0.6 mg/kg/d PO for 2 d | Croup<br>Acute asthma | |
| fluticasone (Flovent®) | Moderate dose – 250-500 µg/d divided bid<br>High dose – >500 µg/d divided bid | Asthma | |
| ibuprofen | 5-10 mg/kg/dose PO q6-8h | Analgesic, antipyretic | Cautious use in patients with liver impairment, history of GI bleeding or ulcers |
| iron | 6 mg/kg/d elemental iron OD or divided tid | Anemia | SE: dark stool, constipation, dark urine |
| polyethylene glycol 3350 (PEG) | Disimpaction: 1-1.5 g/kg/d x 3 d<br>Maintenance: starting dose at 0.4-1 g/kg | | |
| prednisone/ prednisilone | 1-2 mg/kg/d PO x 5 d<br>3-4 mg/kg/d PO then taper to 1-2 mg/kg/d<br>PO once platelet count >30 x $10^9$/L<br>60 mg/$m^2$/d PO | Asthma<br>ITP<br>Nephrotic syndrome | Oral prednisone is bitter tasting, consider using prednisilone |
| salbutamol (Ventolin®) | 0.01-0.03 mL/kg/dose in 3 mL NS via nebulizer q0.5-4h prn<br>100-200 µg/dose prn, max 4-8 puffs frequency q4h | Acute asthma<br>Maintenance treatment for asthma | Can cause tachycardia, hypokalemia, restlessness |

Source: Lau E. (2009) The 2010-2011 Formulary – The Hospital for Sick Children

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**Web-Based Resources**

http://www.medscape.com/home/topics/pediatrics.
http://www.icondata.com/health/pedbase.
http://www.cda-adc.ca.
http://www.aboutkidshealth.ca.
http://www.healthychildren.org.
http://www.publichealth.gc.ca.
http://www.cps.ca.
www.uptodate.com.

# PL Plastic Surgery

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# Acronyms

| | |
|---|---|
| ABI | ankle-brachial index |
| ABG | arterial blood gas |
| AIN | anterior interosseous nerve |
| APL | abductor pollicis longus |
| ARDS | acute respiratory distress syndrome |
| ATLS | advanced trauma life support |
| BiALCL | breast implant-associated anaplastic large cell lymphoma |
| BMR | basal metabolic rate |
| CHF | congestive heart failure |
| CK | creatine kinase |
| CMC | carpometacarpal |
| CO | carbon monoxide |
| CSF | cerebrospinal fluid |
| CVD | cerebrovascular disease |
| CXR | chest x-ray |
| D5W | 5% dextrose in water |
| DIEP | deep inferior epigastric perforator |
| DIP | distal interphalangeal joint |
| DM | diabetes mellitus |
| EMG | electromyography |
| ENT | ear, nose, throat |
| EOM | extraocular movement |
| EPB | extensor pollicis brevis |
| FDP | flexor digitorum profundus |
| FDS | flexor digitorum superficialis |
| FTSG | full thickness skin graft |
| GBS | group B Streptococcus |
| HTN | hypertension |
| I&D | incision and drainage |
| ICP | intracranial pressure |
| ICU | intensive care unit |
| IGAP | inferior gluteal artery perforator |
| IP | interphalangeal |
| IVIg | intravenous immunoglobulin |
| MC | metacarpal |
| MCP | metacarpophalangeal joint |
| NAC | nipple-areola complex |
| NCV | nerve conduction velocity |
| NPWT | negative pressure wound therapy |
| NS | normal saline |
| NSAID | nonsteroidal anti-inflammatory drug |
| OM | otitis media |
| OR | operating room |
| ORIF | open reduction internal fixation |
| OT | occupational therapy |
| PIP | proximal interphalangeal joint |
| PMN | polymorphonuclear |
| PT | physiotherapy |
| PVD | peripheral vascular disease |
| RA | rheumatoid arthritis |
| RL | Ringer's lactate |
| ROM | range of motion |
| SGAP | superior gluteal artery perforator |
| SIADH | syndrome of inappropriate antidiuretic hormone |
| SIEA | superficial inferior epigastric artery |
| SLP | speech-language pathology |
| SOF | superior orbital fissure |
| STSG | split thickness skin graft |
| TBSA | total body surface area |
| TMJ | temporomandibular joint |
| TRAM | transverse rectus abdominis myocutaneous |
| UCL | ulnar collateral ligament |
| UV | ultraviolet |

# Basic Anatomy Review

## Skin

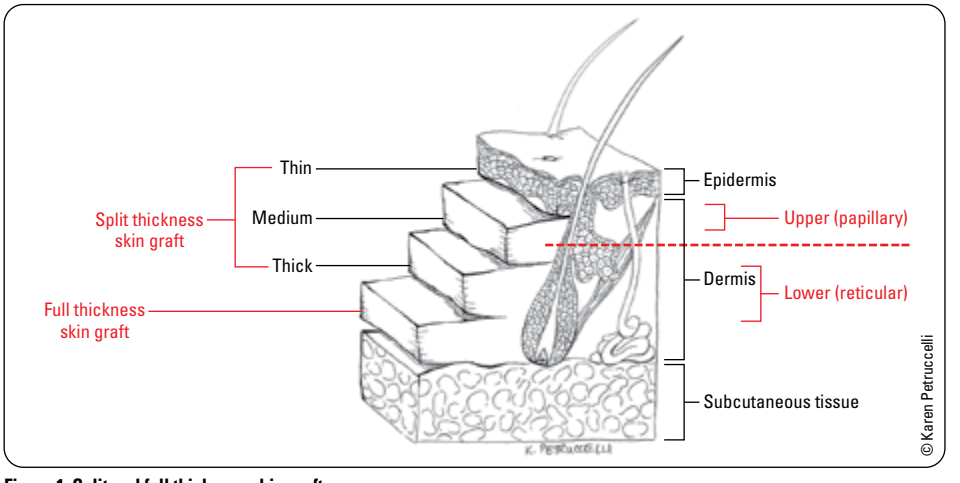



**Figure 1. Split and full thickness skin grafts**

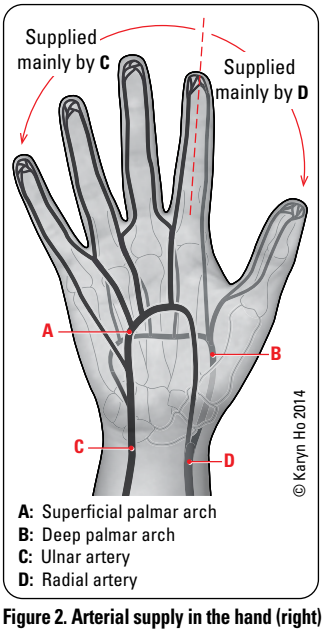



**Figure 2. Arterial supply in the hand (right)**

## Hand

### BONES AND NERVES

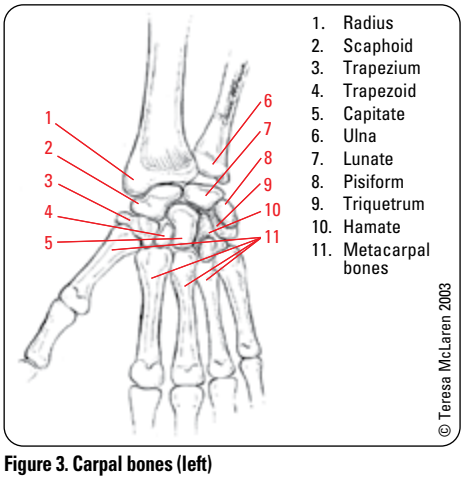



**Figure 3. Carpal bones (left)**

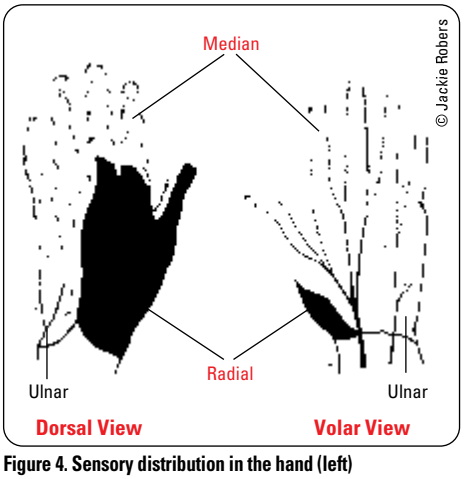



**Figure 4. Sensory distribution in the hand (left)**

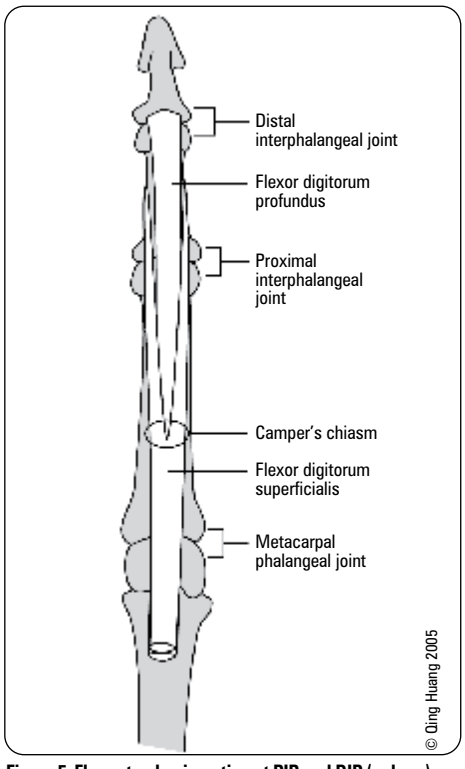



**Figure 5. Flexor tendon insertion at PIP and DIP (palmar)**

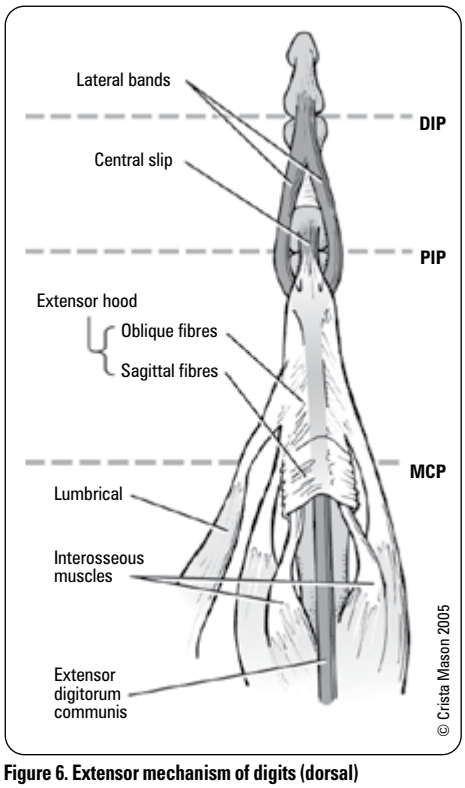



**Figure 6. Extensor mechanism of digits (dorsal)**

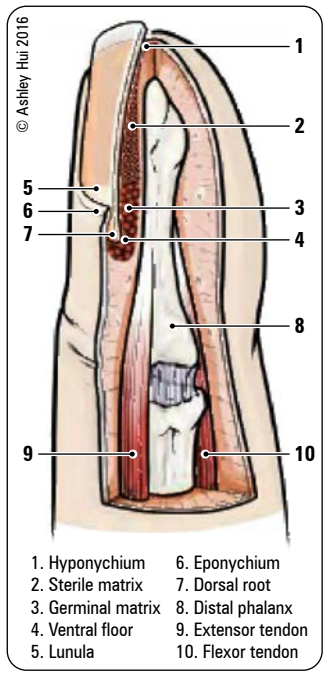



**Figure 7. Nail anatomy**

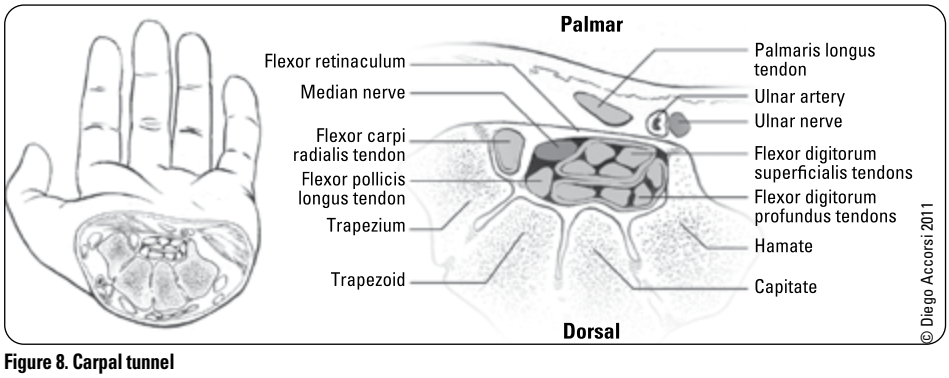


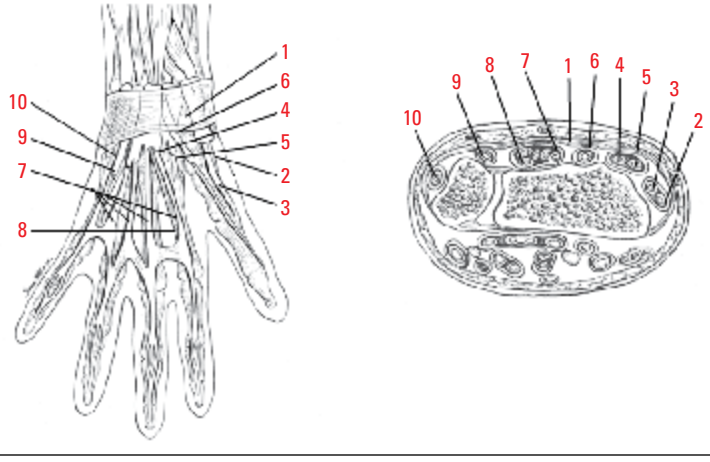

**Figure 8. Carpal tunnel**

**Flexor Tendons**
All require OR repair

**Extensor Tendons**
ER repair unless proximal/multiple tendons

**Carpal Bone Mnemonic**

**So Long to Pinky. Here Comes The Thumb.**
**S**caphoid
**L**unate
**T**riquetrum
**P**isiform
**H**amate
**C**apitate
**T**rapezoid
**T**rapezium




1. Extensor retinaculum

**Compartment 1**
2. Abductor pollicis longus
3. Extensor pollicis brevis

**Compartment 2**
4. Extensor carpi radialis brevis
5. Extensor carpi radialis longus

**Compartment 3**
6. Extensor pollicis longus
   (EPL tendon passes around Lister's tubercle)

**Compartment 4**
7. Extensor digitorum
8. Extensor indicis

**Compartment 5**
9. Extensor digiti minimi

**Compartment 6**
10. Extensor carpi ulnaris

**Figure 9. Extensor compartment of the wrist** (dorsal view and cross-sectional view)

# Brachial Plexus

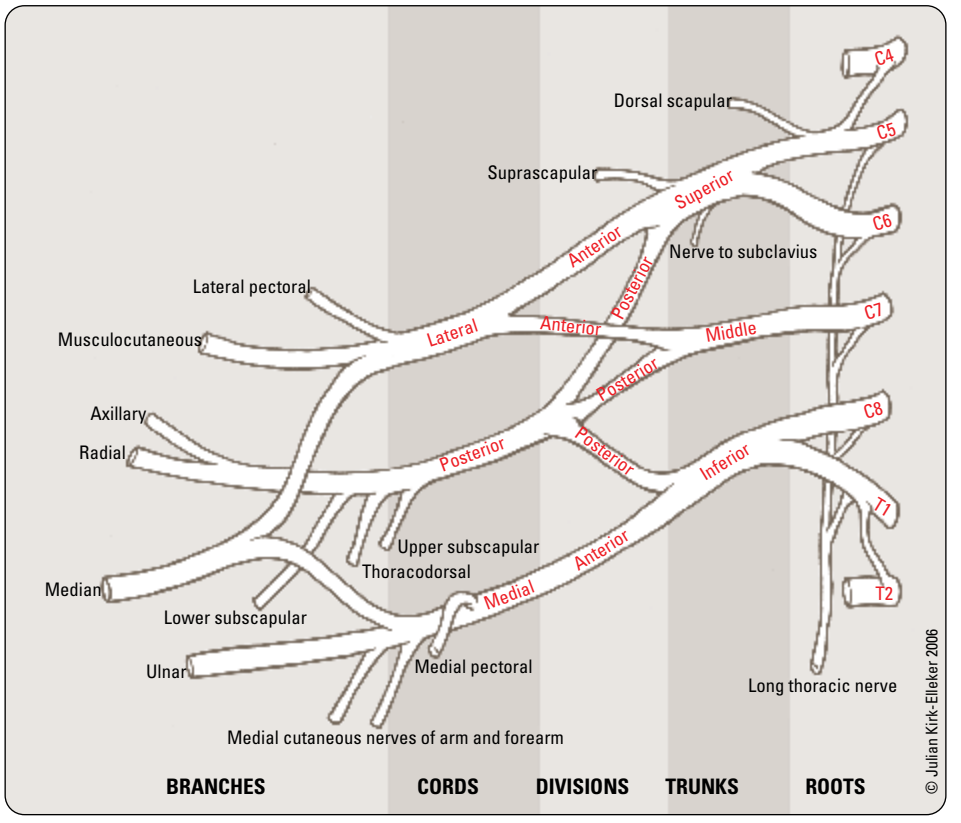



**Figure 10. Brachial plexus anatomy**

**Brachial Plexus**

**Rob Thomas Drinks Cold Beers**
**R**oots
**T**runks
**D**ivisions
**C**ords
**B**ranches

# Face

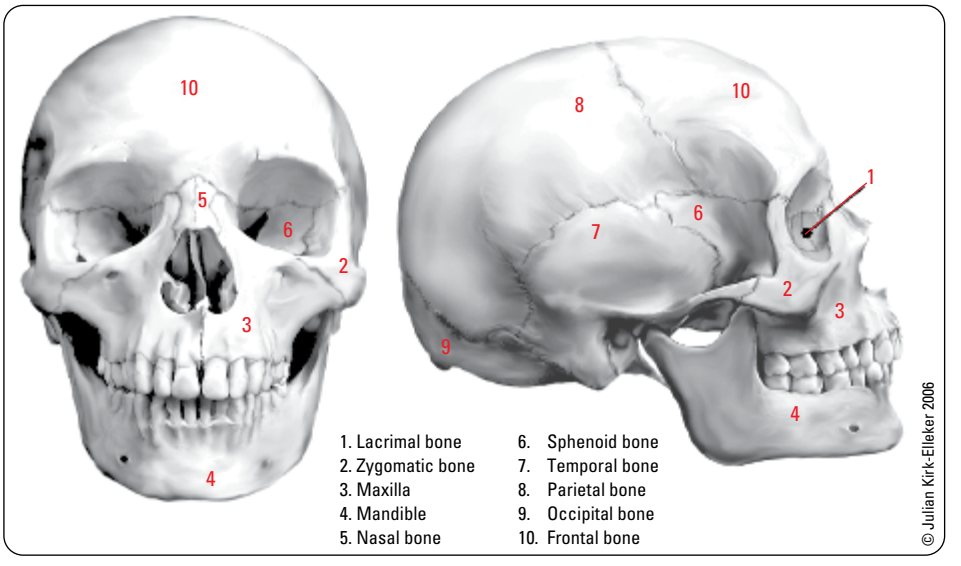



**Figure 11. Skull and facial bones**

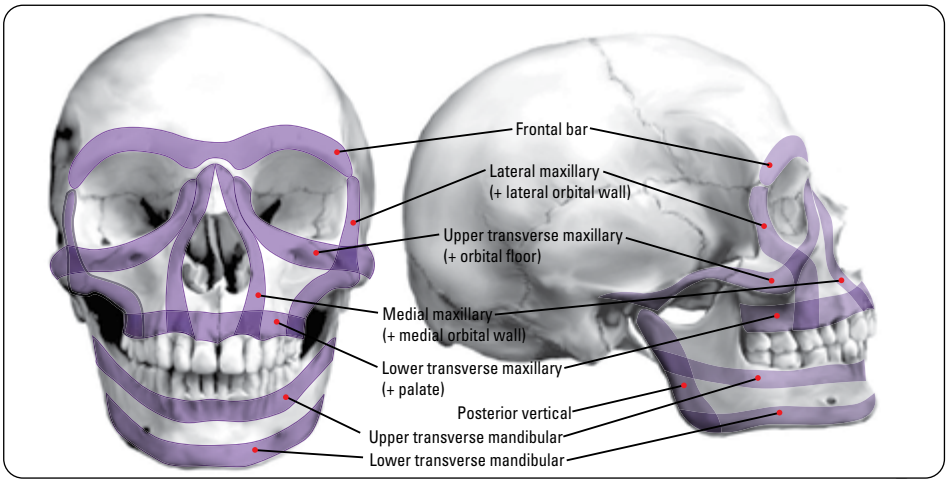



**Figure 12. Craniofacial horizontal and vertical buttresses**

# Skin Lesions and Masses

## Differential Diagnosis of Skin Lesions/Masses

- for background information and medical management (see Dermatology, D5)
- for biopsy techniques, see *Skin Biopsy Types and Techniques*, PL7

## Surgical Management of Malignant Skin Lesions

- surgical treatment for all malignant skin lesions involve total excision of the primary lesion
- for pathophysiology and diagnosis see Dermatology, D34-37
- excision margin of lesion depends on the type of lesion, the lesion diameter, and (for melanoma) the lesion depth
- for decisions regarding reconstruction using flaps or skin grafts, see *Reconstruction*, PL12

### Precursors of Malignant Lesions

**Table 1. Precursors**

| Basal Cell Carcinoma | Squamous Cell Carcinoma | Malignant Melanoma |
|---|---|---|
| Nevus sebaceous of Jadassohn | Actinic keratosis<br>Bowen's disease<br>Bowenoid papulosis<br>Leukoplakia<br>Erythroplasia | Lentigo maligna<br>Giant congenital nevus<br>Dysplastic nevus |

### Surgical Margins

**Table 2. Surgical Margins for Basal Cell Carcinoma**

| Type of Lesion | Surgical Margins |
|---|---|
| Low Risk | >5 mm* |
| High Risk** | >10 mm |

*3-5 mm margin may be acceptable for aesthetically sensitive areas (e.g. eyelid)
**High risk features include: diameter and location (>20 mm trunk, >6 mm face, hands, and feet), poorly defined borders, recurrent lesion, poor differentiation, and type of lesion (e.g. sclerosing BCC), determined via initial biopsy

**Table 3. Surgical Margins for Squamous Cell Carcinoma**

| Type of Lesion | Surgical Margins |
|---|---|
| Low Risk | >5 mm |
| High Risk* | >10 mm |

*High risk features include: depth >2 mm, facial lesions, poorly defined borders, recurrent lesion, perineural invasion, poor differentiation, and type of lesion (e.g. morpheoform), determined via biopsy

**Table 4. Surgical Margins for Malignant Melanoma**

| Depth of Lesion* | Surgical Margins |
|---|---|
| *In situ* | 0.5 cm |
| <1 mm | 1 cm |
| 1-1.99 mm | 1-2 cm |
| ≥2 mm | 2 cm** |

*Determined via biopsy **Or more as long as it doesn't interfere with reconstruction

# Basic Surgical Techniques

## Sutures and Suturing

### ANESTHESIA

- irrigate before injecting anesthetic, followed by debridement and more vigorous irrigation

**Table 5. Toxic Limit and Duration of Action (1 cc of 1% solution contains 10 mg lidocaine)**

| | Without Epinephrine | With Epinephrine (vasoconstrictor, limits bleeding) |
|---|---|---|
| Lidocaine (Xylocaine®)* | 5 mg/kg, lasts 45-60 min | 7 mg/kg, lasts 2-6 h |
| Bupivicaine (Marcaine®) | 2 mg/kg, lasts 2-4 h | 3 mg/kg, lasts 3-7 h |

* Lidocaine toxicity symptoms include: circumoral numbness, light-headedness, and drowsiness followed by tremors and seizures. Cardiac and respiratory signs are late findings

- for example, when using 1% lidocaine without epinephrine in a 70 kg patient:
  - toxic limit = 5 mg/kg x 70 kg = 350 mg
  - max bolus injection = 350 mg ÷ 10 mg/cc = 35 cc (may add more after 30 min)

### IRRIGATION AND DEBRIDEMENT

- irrigate copiously with a physiologic solution such as Ringer's lactate or normal saline to remove surface clots, foreign material, and bacteria
- debride all obviously devitalized tissue; irregular or ragged wounds must be excised to produce sharp wound edges that will assist healing when approximated
- wounds left unapproximated ≥8 h should be debrided and copiously irrigated to ensure wound edges are optimized for healing
- there is high risk of infection for any wound closed primarily after 8 h

### SUTURES

- use of a particular suture material is dependent on surgeon preference; however, skin should be closed with a non-absorbable, monofilament suture material when traumatic mechanisms are involved to prevent harboring bacteria in suture material

**Table 6. Suture Materials: Absorbable vs. Non-absorbable and Monofilament vs. Multifilament**

| Suture Materials | Uses | Examples | Notes |
|---|---|---|---|
| **Absorbable** | Deep sutures under short-term tension<br>Skin closure in children | Plain gut®, Vicryl®, Polysorb®, Biosyn®, Monocryl®, Caprosyn®, chromic gut, fast absorbing gut | Loses at least 50% of their strength in 4 wk; eventually absorbed |
| **Non-absorbable** | Skin closure<br>Sites of long-term tension | Nylon, polypropylene (Prolene®), stainless steel, silk, Ticron®, Ethibond® | Lower likelihood of wound dehiscence, more difficult to tie, makes track marks |
| **Monofilament** | Everyday use and optimal for contaminated and infected wounds (lower likelihood of bacterial trapping in suture material) | Monosof®, Monocryl®, Biosyn®, Prolene® | Slides through tissue with less friction; more memory/stiffness; more difficult to tie; requires multiple throws (lower knot security) |
| **Multifilament** | AVOID in contaminated wounds (increased likelihood of bacterial trapping) | Vicryl® and silk, Ticron®, Ethibond® | Less memory/stiffness, thus easier to work with (higher knot security) |

### BASIC SUTURING TECHNIQUES

#### Basic Suture Methods

- simple interrupted: can be used in almost all situations
- sub-cuticular: good cosmetic result but weak, used in combination with deep sutures; not used in trauma
- vertical / horizontal mattress: for areas difficult to evert (e.g. volar hand)
- continuous over and over (i.e. "running", "baseball stitch"): time-saving, good for hemostasis
- deep / buried dermal: simple interrupted sutures placed in dermal layer, reduces skin tension for improved healing

#### Other Skin Closure Materials

- tapes: may be indicated for superficial wounds and those with opposable edges; tape cannot be used on actively bleeding wounds; when placed across the incision, will prevent surface marks and can be used as the primary closing material or as additional reinforcement after primary surface sutures have been removed
- skin adhesives: e.g. 2-octyl cyanoacrylate (e.g. Dermabond®) works well on small areas without much tension or shearing; may cause irreversible tattooing if foreign materials are left in the wound
- staples: steel-titanium alloys that incite minimal tissue reaction (healing is comparable to wounds closed by suture)

Traumatic tattoos are permanent discolourations resulting from new skin growth over foreign material or dirt left behind in the dermis. Copious irrigation and debridement should be done ASAP in order to prevent traumatic tattoos, as they are very difficult to treat later

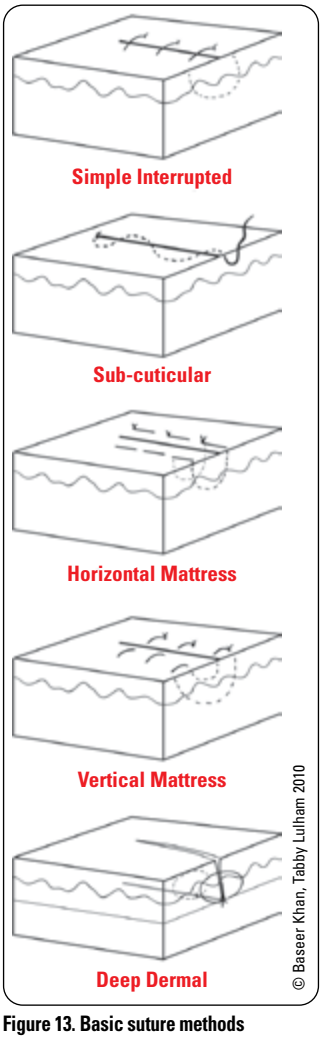



**Figure 13. Basic suture methods**

**Steps to Ensuring Good Suturing Cosmesis**

- Incisions should be made along resting skin tension lines
- Attain close apposition of wound edges
- Minimize tension on skin by closing in layers
- Evert wound edges
- Use appropriately sized suture for skin closure (5-0, 6-0 on face; 3-0, 4-0 elsewhere)
- Ensure equal width and depth of tissue on both sides
- Remove sutures within 5-7 d from the face, 10-14 d from scalp/torso/extremities

# Excision

- plan your incision along resting skin tension lines to minimize appearance of scar
- use elliptical incision to prevent "dog ears" (heaped up skin at end of incision), so the length of the ellipse should be approximately 3x the width
- if needed, undermine skin edges (separate skin from underlying fascia to allow wound edge manipulation and decrease tension)
- use layered closure including deep dermal sutures (decreases tension)

**Resting Skin Tension Lines**
Natural skin/wrinkle lines with minimal linear tension. Placing incisions parallel to resting skin tension lines minimizes widening/hypertrophy and helps to camouflage scars. Resting skin tension lines are usually parallel to any existing wrinkle lines and perpendicular to the orientation of underlying muscle fibres (perpendicular to lines of maximum extensibility)

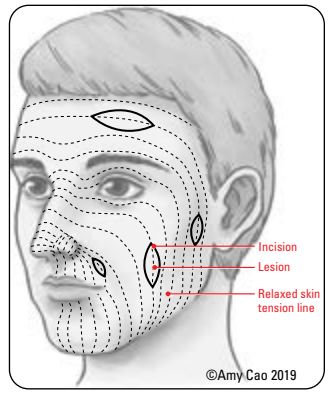



**Figure 14. Incision of lesions along resting skin tension lines**

# Skin Biopsy Types and Techniques

## SHAVE BIOPSY
- used for superficial lesions where sampling of the full thickness of the dermis is not necessary or practical
- most suitable lesions for shave biopsies are benign lesions either elevated above the skin or have pathology confined to the epidermis (e.g. seborrheic or actinic keratoses, skin tags, and warts)
- high risk of recurrence with shave biopsy for any lesions, including actinic or seborrheic keratoses
- rapid, requires little training, and does not require sutures for closure
- heals by secondary intent (moist dressings should be used)
- should not be used for pigmented lesions – an unsuspected melanoma cannot be properly staged if partially removed

## NEEDLE BIOPSY
- 21 G for lymph node biopsy
- Trucut® needle biopsy for breast masses suspected for carcinoma

## INCISIONAL BIOPSY
- can be a punch biopsy, an ellipse within the lesion, or a narrow margin excision of the lesion
- gives pathologists a portion of the lesion and the border with normal skin
- punch biopsies involve the removal of a core-shaped piece of tissue to allow sampling of the deep dermis; performed with round, disposable knives ranging in diameter from 2-10 mm
- punch biopsy wounds can be closed with suture or left to heal by secondary intention. Punches greater than 3 mm may produce scarring and are best closed with one or two sutures

## EXCISIONAL BIOPSY
- performed for lesions that require complete removal for diagnostic purposes
- performed for lesions that cannot be adequately punch biopsied due to size or depth
- for small pigmented lesions and atypical moles; if concerned about melanoma, can do a narrow margin excision for the diagnosis and treatment of small pigmented lesions and atypical moles
- best for small lesions that are easily removed and primarily closed
- requires the greatest amount of expertise and time
- always requires sutures for closure

## TECHNIQUE

### General
- all shave and punch biopsies performed in clinic are done using aseptic technique, but are not sterile
- sterile gloves are indicated for biopsies and excisions in all patients

### Preparing the Site
- common skin antiseptics (Betadine®, chlorhexidine) can be used to prepare the biopsy site
- chlorhexidine is used in concentrations ranging from 0.5-4%. The higher concentration cannot be used on the face, as it could get into the eyes or ears and may burn or cause damage. Most chlorhexidine preps also contain alcohol, which can be flammable, so allow to dry before the biopsy and certainly before using any cautery
- Betadine® (7.5% povidone–iodine) may be safer for the head and neck (as to avoid the above problems with chlorhexidine) and around the eyes and ears
- mark the intended lesion and surgical margins with a surgical marker, since they may be temporarily obliterated following injection of the anesthetic
- for all biopsies, a sterile drape technique is indicated. A fenestrated surgical drape is placed around the biopsy site after the area is cleansed and anesthetized

### Anesthesia
- most commonly used local anesthetic is 1% or 2% lidocaine (with epinephrine)
- small amounts of epinephrine are added to constrict blood vessels, decrease bleeding, prolong anesthesia, and limit lidocaine toxicity. The local with epinephrine can be injected directly into the lesion
- local anesthetics with epinephrine may be used anywhere in the body, including the digits
- vascular compromise is not an abosolute contraindication to epinepherine, but care should be taken when using epinepherine in a small area that has been significantly injured and vascular compromise is suspected (e.g. saw injury involving the digits)
- phentolamine is a reversal agent for epinephrine

# Wounds

- wound: disruption of the normal anatomical relationships of tissue as a result of injury

## Types of Wounds

- laceration: sharply cut tissue
- abrasion: superficial skin layer is removed, variable depth
- contusion: injury caused by forceful blow to the skin and soft tissue; entire outer layer of skin intact, yet injured
- avulsion: skin and soft tissue forcefully separated from deeper structures, potentially compromising blood supply or resulting in full detachment (amputation)
- puncture wounds: cutaneous opening relatively small as compared with depth (e.g. needle), including bite wounds
- crush injuries: caused by compression
- burns: thermal, chemical, electrical
- ulcers

### Principles of Wound Healing

**Table 7. Factors Influencing Wound Healing**

| Local (reversible/controllable) | General (often irreversible) |
|---|---|
| Mechanical (local trauma, significant crush, avulsion, tension) | Age (affects healing rate) |
| Blood supply (ischemia/circulation) | Nutrition |
| Technique and suture materials | Tobacco smoking |
| Retained foreign body | Alcohol consumption |
| Infection | Chronic illness (e.g. DM, cancer, CVD, renal failure) |
| Venous HTN | Immunosuppression (steroids, chemo) |
| Peripheral vascular disease | Tissue irradiation |
| Hematoma/seroma (↑ infection rate) | Genetic predisposition to abnormal healing (e.g. hypertrophic or keloid scarring, collagen vascular disease) |
| | Skin type |

### STAGES OF WOUND HEALING

- growth factors released by tissues play an important role
- scar is mature once it has completed the final stage, usually after 1-2 yr

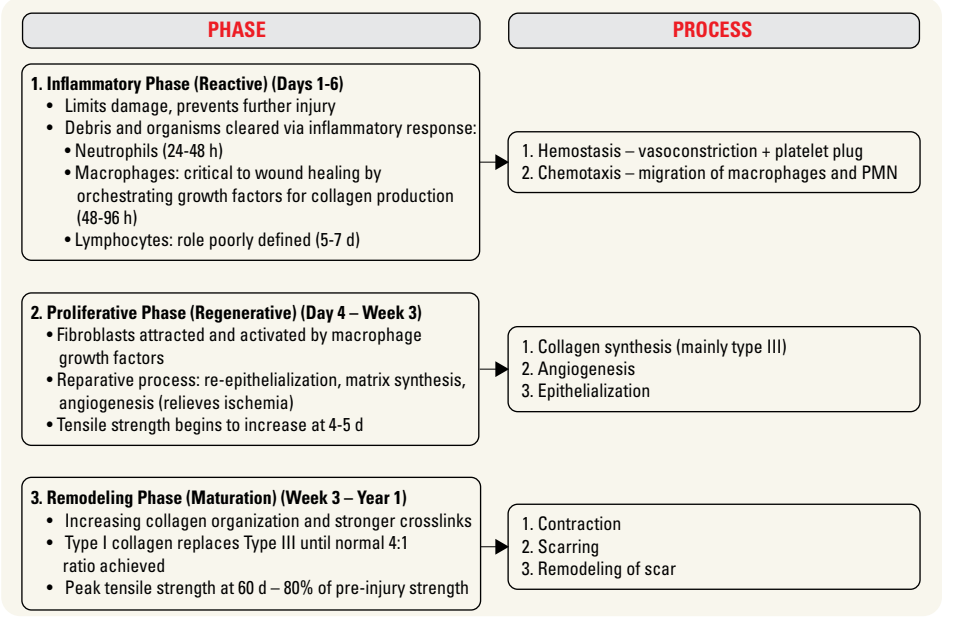



**Figure 15. Stages of wound healing**

## TYPES OF WOUND HEALING

### Primary (1°) Healing (First Intention)
- **definition**: definition: wound closure by direct approximation of edges within hours of wound creation (i.e. with sutures, staples, skin graft, etc.)
- **indication**: recent (<6 h, longer with facial wounds), clean wounds
- **contraindications**: animal/human bites (except on face), crush injuries, infection, long time lapse since injury (>6-8 h), retained foreign body

### Secondary (2°) Healing/Spontaneous Healing (Second Intention)
- **definition**: wound left open to heal spontaneously (epithelialization occurs at 1 mm/d from wound margins in concentric pattern, contraction [myofibroblasts], and granulation) – maintained in inflammatory phase until wound closed; requires dressing changes; inferior cosmetic result
- **indication**: when 1° closure not possible or indicated (see *Primary Healing*)

Myofibroblasts are the cells responsible for wound contraction; they do this at a rate of less than 0.75 mm/d

### Tertiary (3°) Healing/Delayed Primary Healing (Third Intention)
- **definition**: intentionally interrupt healing process (e.g. with packing, sharp debridement), then wound can be closed primarily at 4-10 d post-injury after granulation tissue has formed and there is $<10^5$ bacteria/gram of tissue
- **indication**: contaminated (high bacterial count), long time lapse since initial injury, severe crush component with significant tissue devitalization, closure of fasciotomy wounds
- prolongation of inflammatory phase decreases bacterial count and lessens chance of infection after closure

## ABNORMAL HEALING

### Hypertrophic Scar
- **definition**: scar remains roughly within boundaries of original scar
- red, raised, widened, frequently pruritic
- common sites: back, shoulder, sternum
- **treatment**: scar massage, pressure garments, silicone gel sheeting, corticosteroid injection, surgical excision if other options fail (however, may still recur)
- often improve slowly over time

### Keloid Scar
- **definition**: scar grows outside boundaries of original scar
- red, raised, widened, frequently pruritic
- caused by:
  - genetic factors (highest rates in African Americans, Asians)
  - endocrine factors
  - excess tension on wound or delayed closure (as in burn wounds)
- common sites: central chest, back, shoulders, deltoid, ear, angle of mandible
- **treatment**: multimodal therapy including: pressure garments, silicone gel sheeting, corticosteroid injection, surgical excision with post-surgical management if other options fail (however, there is a high chance of recurrence), fractional carbon dioxide ablative laser, radiation

### Spread Scar
- characterized by having exactly the same order of collagen fibres as normal scars
- clinically, a typical spread scar is flat, wide, and often dented
- treatment: surgical excision and closure

### Chronic Wound
- wound fails to achieve primary wound healing within 4-6 wk
- common chronic wounds include: diabetic, pressure, and venous stasis ulcers
- treatment: may heal with meticulous wound care; may also require surgical intervention
- Marjolin's ulcer: squamous cell carcinoma arising in a chronic wound secondary to genetic changes caused by chronic inflammation → always consider biopsy of chronic wound

# Infected Wounds

### Definitions
- the presence of bacteria within a wound may be divided into 4 categories:
  - contamination: the presence of non-replicating microorganisms within a wound
  - colonization: the presence of replicating microorganisms within a wound
  - critical colonization: increasing bacterial burden; have delayed healing but may not exhibit classic signs of infection
  - infection: the presence of $>10^5$ microorganisms in a wound without intact epithelium or small amounts of a very virulent organism (e.g. GBS); have delayed healing and exhibit classic signs of infection
    - signs of infection: redness, swelling, pain, clinically unwell

**Risk Factors for Infection**
- Virulence of the infecting microorganism
- Amount of bacteria present
- Host resistance
- Immunocompromised host

## Management of Acute Contaminated Wound (<24 h)

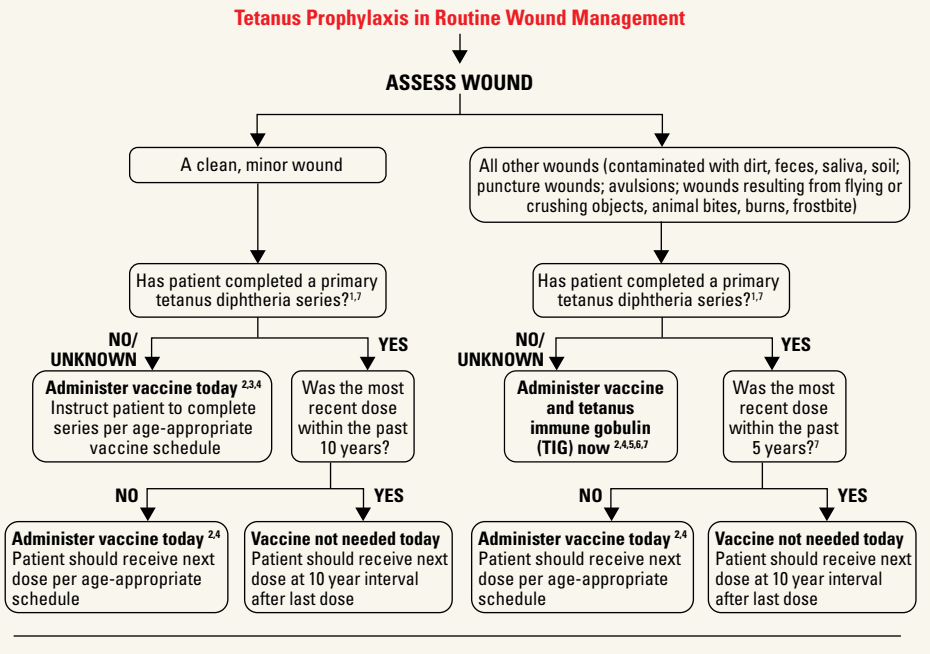
- cleanse and irrigate open wound with physiologic solution (NS or RL) using sufficient pressure
- evaluate for injury to underlying structures (vessels, nerve, tendon, and bone)
- control active bleeding; previously closed wounds may require suture removal in order to drain any pus and allow for thorough irrigation and debridement
- debridement: removal of foreign material, devitalized tissue, old blood
  - surgical debridement: blade and irrigation if indicated
- tetanus prophylaxis ± post-exposure treatment of:
  - hepatitis B, HIV, hepatitis C (if titres confirmed at 6 mo)
- re-evaluate in 24-48 h for signs of superficial or deep infection
  - if evidence of infection (i.e. erythema, warmth, pain, discharge), open infected portion of wound by removing sutures, swab sample for culture and sensitivity, irrigate wound and allow healing by secondary intention
  - risk factors for infection include: wound >8 h, severely contaminated, human/animal bites, immunocompromised, involvement of deeper structures (e.g. joints, fractures)
  - use systemic antibiotics if wound cultures are positive and there are signs of infection

## Management of Late Contaminated Wounds (>24 h, including ulcers)

- tetanus prophylaxis
- irrigation and debridement
  - traumatic tattooing can occur if foreign materials left in wound
- systemic antibiotics if wound cultures are positive and there are signs of infection
- closure: final closure via secondary intention (most common), delayed wound closure (3° closure), skin graft, or flap; successful closure depends on bacterial count of ≤$10^5$/$cm^3$ prior to closure and frequent dressing changes

**Wound Exudate Characteristics**

- Serous drainage (plasma): thin; clear or light yellowish
- Sanguineous drainage (fresh blood): bright red
- Serosanguineous drainage (mix of blood and serous fluid): thin and watery; pale red to pink
- Purulent drainage (infection): thick and opaque; white, yellow, or pale green




[1] A primary series consists of a minimum of 3 doses of tetanus- and diphtheria- containing vaccine (DTaP/DTP/Tdap/DT/Td)

[2] Age-appropriate vaccine:
- DTaP for infants and children 6 weeks up to 7 years of age (or DT pediatric if pertussis vaccine is contraindicated);
- Tetanus-diphtheria (Td) toxoid for persons 7-9 years of age; and ≥65 years of age;
- Tdap for persons 10-64 years of age if using Adacel™‡ or ≥10 years of age if using Boostrix™‡, unless the person has received a prior dose of Tdap*

[3] No vaccine or TIG is recommended for infants <6 weeks of age with clean, minor wounds (and no vaccine is licensed for infants <6 weeks of age)

[4] **Tdap*** is preferred for persons 10-64 years of age if using Adacel™‡ or ≥10 years of age if using Boostrix™‡ who have never received Tdap.
Td is preferred to tetanus toxoid (TT) for persons 7-9 years of age, or ≥65 years of age if only Adacel™‡ is available, or those who have received a Tdap previously. If TT is administered, an adsorbed TT product is preferred to fluid TT (all DTaP/DTP/T-dap/DT/Td products contain adsorbed tetanus toxoid)

[5] Give TIG 250 U IM for all ages. It can and should be given simultaneously with the tetanus-containing vaccine

[6] For infants <6 weeks of age, TIG (without vaccine) is recommended for "dirty" wounds (wounds other than clean, minor)

[7] Persons who are HIV positive should receive TIG regardless of tetanus immunization history

* Tdap vaccines:
- Adacel™ (Sanofi) is licensed for persons 10-64 years of age
- Boostrix™ (GSK) is licensed for persons ≥10 years of age

‡ Brand names are used for the purpose of clarifying product characteristics and are not in any way an endorsement of either product

**Figure 16. Tetanus immunization recommendations**

**Table 8. Risks for Tetanus Infection**

| Wound Characteristics | Tetanus-Prone | Not Tetanus-Prone |
|---|---|---|
| **Time since injury** | >6 h | <6 h |
| **Depth of injury** | >1 cm | <1 cm |
| **Mechanism of Injury** | Crush, burn, gunshot, frostbite, puncture through clothing, farming injury | Sharp cut (e.g. clean knife, clean glass) |
| **Devitalized tissue** | Present | Not present |
| **Contamination** (e.g. soil, dirt, saliva, grass) | Yes | No |
| **Retained foreign body** | Yes | No |

### BITES

- see Emergency Medicine, ER47

### Dog and Cat Bites

- pathogens: *Pasteurella multocida, S. aureus, S. viridans*
- **investigations**
  - radiographs prior to therapy to rule out foreign body (e.g. tooth) or fracture
  - culture for aerobic and anaerobic organisms, Gram stain
- **treatment**: Clavulin® (amoxicillin + clavulanic acid) 500 mg PO q8h started immediately
  - consider rabies prophylaxis if animal has symptoms of rabies or unknown animal
    - ± rabies Ig (20 IU/kg around wound, or IM) and 1 of the 3 types of rabies vaccines (1.0 mL IM in deltoid, repeat on days 3, 7, 14, 28)
- aggressive irrigation with debridement
- healing by secondary intention is mainstay of treatment
- only consider primary closure for bite wounds on the face; otherwise primary closure is contraindicated
- contact Public Health if animal status unknown

### Human Bites

- pathogens: *Staphylococcus* > *β-hemolytic Streptococcus* > *Eikenella corrodens* > *Bacteroides*
- mechanism: most commonly over dorsal MCP from a punch in mouth; "fight-bite"
- serious, as mouth has 109 microorganisms/mL, which get trapped in joint space when fist unclenches and overlying skin forms an air-tight covering ideal for anaerobic growth – can lead to septic arthritis
- **investigations**
  - radiographs prior to therapy to rule out foreign body (e.g. tooth) or fracture
  - culture for aerobic and anaerobic organisms, Gram stain
- **treatment**
  - urgent surgical exploration of joint, drainage, and debridement of infected tissue
  - wound must be copiously irrigated
  - Clavulin® 500 mg PO q8h or (if penicillin allergy) clindamycin 300 mg PO q6h + ciprofloxacin 500 mg PO q12h + secondary closure
  - splint

## Dressings

- dressing selection depends on the wound characteristics and surgeon preference
  - as the wound progresses through healing, it will require different types of dressings; therefore, routine inspection is recommended
    - principles of dressing clean vs. infected wounds
      - clean wounds can be dressed with non-adherent dressing (which is non-adhering to epithelializing tissue); requires secondary dressing
      - infected wounds may need debridement, antibiotics, and antimicrobial dressings (i.e. iodine gauze and silver-containing dressings)
    - moist vs. dry wounds
      - purpose of dressings should be to promote moist wound healing i.e. moistening dry wounds or drying (removing excess exudate/blood) wet wounds
    - wide-based vs. cavitary/tunneling wounds
      - cavitary or tunneling wounds (i.e. through a fascial layer) can be packed with dressing materials (see Table 9) such as hydrogels or Betadine®-soaked ribbon gauze (infected)
    - negative pressure wound therapy (e.g. vacuum-assisted closure) uses sealed vacuum dressings that suction wound fluid and promote increased blood flow to enhance the healing process

**Table 9. Recommended Dressings for Wound Type**

| Wound Depth | Exudate Level | Dressing Material |
|---|---|---|
| **Superficial** | Lightly exuding | Films (Opsite®), hydrogels (Intrasite®, Nu-gel®, Duoderm®) |
| | Any exudate level | Contact layers |
| **Deep** | Light to moderately exuding wounds | Amorphous gels, hydrogels, hydrocolloids (Duoderm®, Tegaderm®), collagen, hypertonic saline gauze (Mesalt®) |
| | Moderately to heavily exuding wounds | Foams (Mepilex®, Allevyn®), alginates (Sorbsan®, Kalto-stat®), hypertonic saline gauze, hydrofibre (Aquacel®) |

Adapted from Grabb & Smith's Plastic Surgery, 6th ed. Chapter 3, Table 3.3

# Reconstruction

## RECONSTRUCTION LADDER

### Definition
- an approach to wound management with successively more complex methods of treatment
- surgeons should start with the least complex method and progressively increase in complexity as appropriate

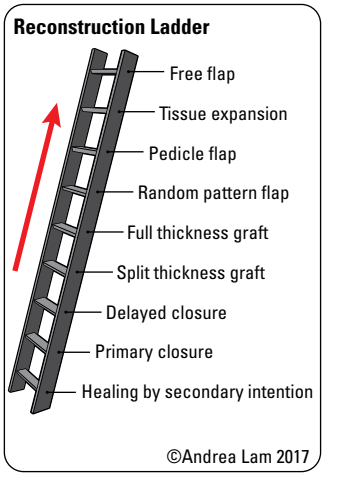



**Figure 17. Reconstructive ladder - in order of increasing complexity**

## SKIN GRAFTS

### Definition
- tissue composed of epidermis and varying degrees of dermis, that does not carry its own blood supply. Survival requires the generation of new blood vessels from the recipient site bed

### Donor Site Selection
- must consider size, hair pattern, texture, thickness of skin, and colour (facial grafts best if taken from "blush zones" - harvest sites above clavicle where colour match for full thickness grafts is optimized e.g. pre/post auricular or neck)
- partial thickness grafts usually taken from inconspicuous areas (e.g. buttocks, lateral thighs, etc.)

### Partial Thickness Skin Graft Survival
- 3 phases of skin graft "take"
  1. plasmatic imbibition: diffusion of nutrition from recipient site (first 48 h)
  2. inosculation: vessels in graft connect with those in recipient bed (d 2-3)
  3. neovascular ingrowth: graft revascularized (d 3-5)
- requirements for graft survival
  - well-vascularized bed (recipient site). Unsuitable beds include: bone, tendon, heavily irradiated, infected wounds, etc.
  - coagulation begins as soon as graft is placed on bed
  - good contact between graft and recipient bed. Staples, sutures, splinting, and pressure dressings are used to prevent movement/ shearing of graft and hematoma or seroma formation
  - fibrin glue used to enhance fixation
  - low bacterial count at recipient site ($<105/cm^3$, to prevent infection)
- common reasons for graft loss: hematoma/seroma, infection, mechanical force (e.g. shearing, pressure)

### Classification of Skin Grafts
1. by species
   - autograft: from same individual
   - allograft (homograft): from same species, different individual
   - xenograft (heterograft): from different species (e.g. porcine)
2. by thickness: see Table 10

**Table 10. Skin Grafts**

| | Split Thickness Skin Graft | Full Thickness Skin Graft |
|---|---|---|
| **Definition** | Epidermis and part of dermis | Epidermis and all of dermis |
| **Donor Site** | More sites | Donor sites limited by the ability to use primary closure |
| **Healing of Donor Site** | Re-epithelialization via dermal appendages in graft and wound edges | Primary closure |
| **Re-Harvesting** | ~10 d (faster on scalp) | N/A |
| **Graft Take** | More reliable and better survival; shorter nutrient diffusion distance | Lower rate of survival (thicker, slower vascularization) |
| **Contraction*** | Less 1° contraction, greater 2° contraction (less with thicker graft) | Greater 1° contraction, less 2° contraction |
| **Aesthetic** | Poor | Good |
| **Comments** | Allows for extravasation of blood/serum | May use on face and fingers |
| **Advantages** | Takes well in less favourable conditions<br>Can cover a larger area<br>Can be meshed for greater area<br>Allows for extravasation of blood/serum<br>Large number of donor sites | Resists contraction, better colour match<br>May use on face and fingers |
| **Disadvantages** | Contracts significantly, abnormal pigmentation, high susceptibility to trauma | Requires well vascularized bed |
| **Uses** | Large areas of skin, granulating tissue beds | Face (colour match), site where thick skin or decreased contracture is desired (e.g. finger) |

*1° contraction: immediate reduction in size upon harvesting; 2° contraction: reduction in size once graft placed on wound bed and healing has occurred

### Meshed Grafts (split thickness grafts can be meshed after harvest by a mesher to a variety of ratios)

- **advantages**
  - prevents accumulation of fluids (e.g. hematoma, seroma)
  - covers a larger area
  - best for contaminated recipient site
- **disadvantages**
  - poor cosmesis ("alligator hide" appearance)
  - has greater secondary contraction than full thickness grafts (see Table 10)

## OTHER GRAFTS

**Table 11. Various Tissue Grafts**

| Graft Type | Use | Preferred Donor Site |
|---|---|---|
| **Bone** | Repair rigid defects | Cranial, rib, iliac, fibula, scapula |
| **Cartilage** | Restore contour of ear and nose | Ear, nasal septum, costal cartilage |
| **Tendon** | Repair or replace a damaged tendon | Palmaris longus, plantaris (present in 85% of population) |
| **Nerve** | Conduit for regeneration across nerve gap | Sural, antebrachial cutaneous, medial brachial cutaneous |
| **Vessel** | Bridge vascular gaps | Forearm or foot vessels for small vessels, saphenous vein for larger vessels |
| **Dermis** | Contour restoration (± fat for bulk) | Thick skin of buttock or abdomen |
| **Fat** | Contour restoration | Abdomen, any area with fat available |
| **Nipple** | To create a new nipple on a reconstructed breast | Nipple |

## FLAPS

- **definition**: tissue of varying composition (skin and fat, muscle and fat, bone and fat, muscle only, etc.), that has a known blood supply (random, pedicled, or named); not dependent on neovascularization, unlike a graft
- may consist of: skin, subcutaneous tissue, fascia, muscle, tendon, bone, other tissue (e.g. omentum)
- **classification**: based on tissue composition, blood supply to skin (random, axial), and location of the donor site (local, regional, distant)
- **indications for flaps**
  - replaces tissue loss due to trauma or surgery (reconstruction)
  - provides skin and temporary soft tissue coverage through which surgery can be carried out later
  - to aid healing or treatment of infection by providing vascularized tissue to a poorly vascularized bed
- **complications**: flap loss due to hematoma, seroma, infection, poor flap design, extrinsic compression (dressing too tight) or vascular failure/thrombosis, fat necrosis (in free and pedicled flaps)

## Random Pattern Flaps

- blood supply by dermal and subdermal plexus to skin and subdermal tissue with random vascular supply
- limited length:width ratio to ensure adequate blood supply (typically 3:1 in the head and neck, 1-2:1 elsewhere)
- flap choice is often a combination of available tissue, type of tissue needed, location of reconstruction site with respect to donor site, blood supply, ability to close the donor site, and surgeon preference
- **types**
  - **rotation**: semicircular tissue rotated around a pivot point for defect closure; commonly used on sacral pressure sores, scalp, and cheek defects
  - **transposition**: tissue is transposed (i.e. lifted up from its native location and brought into the defect) around a pivot point from one location to another; commonly used on certain areas of the face using adjacent areas of excess skin laxity
  - **Z-plasty**: two triangular flaps are repositioned; used to reorient a scar, lengthen the line of a scar, or to break up a scar
  - **advancement flaps (V-Y, Y-V):** defect is closed with uni-directional tissue advancement
    - **single/bipedicle V-Y flaps**: wounds with lax surrounding tissue; the pedicle is the deep tissue underlying the flap

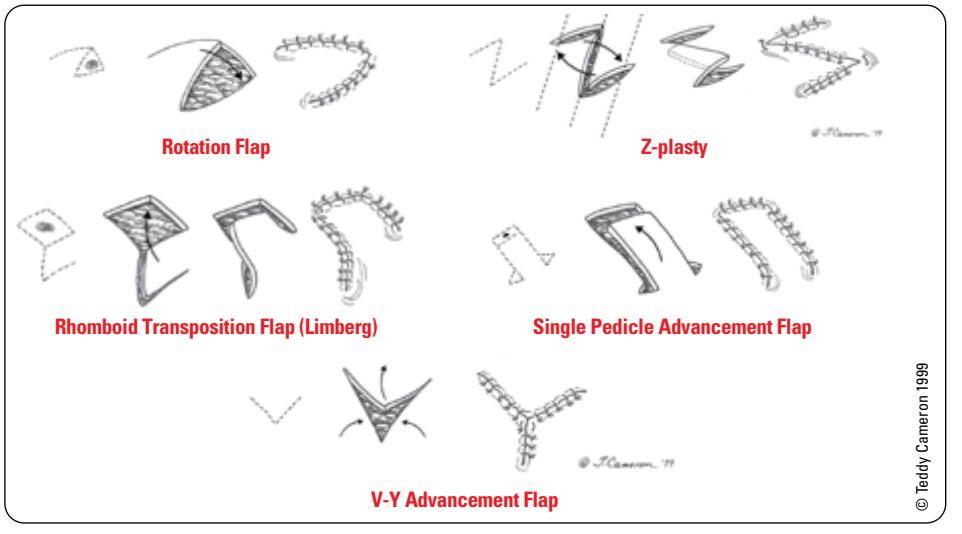



**Figure 18. Wound care flaps – random pattern**

## Axial Pattern Flaps (Arterialized)

- flap contains a well-defined artery and vein
- allows greater length:width ratio (5-6:1)
- **types**
  - **peninsular flap**: skin and vessel intact in pedicle
  - **island flap**: vessel remains intact, but is skeletonized such that the pedicle is better defined
  - **free flap**: segment of tissue with named blood supply (artery and vein) that can be harvested with that blood supply and re-anastomosed in a different anatomical location by microsurgical techniques
- can be sub-classified according to categories such as tissue type, blood supply type, and calibre of vessels
  - e.g. musculocutaneous/myocutaneous (e.g. transverse rectus abdominal myocutaneous) vs. fasciocutaneous

## Free Flaps

- transplanting expendable donor tissue from one part of the body to another by isolating and dividing a dominant artery and vein to a flap, and performing a microsurgical anastomosis between these and the vessels in the recipient wound
- survival rates >95%
- **types**: muscle and skin (common), bone, jejunum, omentum, fascia
- e.g. radial forearm, scapular, latissimus dorsi

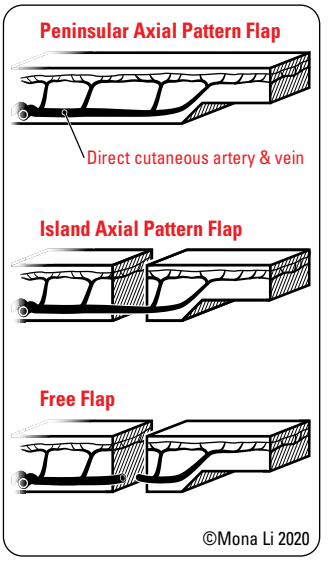



**Figure 19. Axial/arterial pattern skin flaps**

**Table 12. Characteristics of Healthy Free Flap**

| Characteristic | Normal | Arterial Insufficiency | Venous Insufficiency |
|---|---|---|---|
| **Colour** | Pink | Pale | Purple or blue |
| **Temperature** | Warm | Cool | Warm or cool |
| **Arterial Pulse (Doppler)** | + | – | ± |
| **Turgor** | Soft, but with some firmness | Decreased tissue firmness | Increased (tissue firmness with tissue stiffness) |
| **Capillary Refill** | 2-5 s | >5 s | <2 s |

# Soft Tissue Infections

## Erysipelas

### Definition
- acute skin infection of the upper dermis and superficial lymphatics (more superficial than cellulitis)

### Etiology
- typically caused by Group A β-hemolytic *Streptococcus*

### Clinical Features
- intense erythema, induration, and **sharply demarcated borders** (differentiates it from other skin infections)

### Treatment
- penicillin or first-generation cephalosporin (e.g. cefazolin or cephalexin)

## Cellulitis

### Definition
- non-suppurative infection of skin and subcutaneous tissues

### Etiology
- skin flora are most common organisms: *S. aureus*, *β-hemolytic Streptococcus*
- immunocompromised: Gram-negative rods and fungi

### Clinical Features
- source of infection
  - trauma, recent surgery
  - PVD, DM – cracked skin in feet/toes
  - foreign bodies (IV, orthopedic pins)
- systemic symptoms (fever, chills, malaise)
- pain, tenderness, edema, erythema with poorly defined margins, regional lymphadenopathy
- can lead to ascending lymphangitis (visible red streaking in skin proximal to area of cellulitis)

### Investigations
- CBC, blood cultures
- culture and Gram stain a collection/aspirate from wound if open wound
- plain radiographs show soft tissue edema only

### Treatment
- antibiotics: first line – cephalexin 500 mg PO q6h or cloxacillin 500 mg PO q6h x 7 d; if complicated (e.g. lymphangitis, DM, severe infection, oral antibiotic therapy failure), consider IV cefazolin 1-2 g q8h or IV cloxacillin, IV penicillin. All patients should have reassessment in 48 h for resolution if on an oral antibiotic
- outline area of erythema to monitor success of treatment
- immobilize and splint (hands)

## Necrotizing Fasciitis

### Definition
- rapidly spreading, very painful infection of the fascia with necrosis of surrounding tissues
- some bacteria create gas that can be felt as crepitus and can be seen on x-rays
- infection spreads rapidly along deep fascial plane and is limb-and life-threatening

### Etiology
- Type I: polymicrobial (more common in immunocompromised)
- Type II: monomicrobial, usually *β-hemolytic Streptococcus* (more common in healthy patients)

### Risk Factors
- immunocompromised, diabetes mellitus, obesity, IV drug use, age >50 years old

### Clinical Features
- pain out of proportion to clinical findings and beyond border of erythema
- edema, tenderness, ± crepitus (subcutaneous gas from anaerobes), ± flu-like symptoms (e.g. nausea, fever, diarrhea, dizziness, malaise)
- overlying skin changes including blistering and ecchymoses

- patients may look deceptively well at first, but have some physiological abnormalities on intial labs and may rapidly become very sick/toxic
- late findings
  - skin turns dusky blue and black (secondary to thrombosis and necrosis)
  - induration, formation of bullae
  - cutaneous gangrene, subcutaneous emphysema

### Investigations
- a clinical diagnosis
- CT scan only if suspect it is not necrotizing fasciitis (looking for abscess, gas collection, myonecrosis and possible source of infection)
- severely elevated CK: usually means myonecrosis (late sign)
- bedside incision, exploration, and incisional biopsy when ruling out conditions, clinical feature is not supportive, or difficult exam
- during incisional biopsy, often see "dish water pus" (Group A infection) and a hemostat easily passed along fascial plane (fascial biopsy to rule out in equivocal situations)

### Treatment
- vigorous resuscitation (ABCs)
- urgent surgical debridement: remove all necrotic tissue, copious irrigation with plans for repeat surgery in 24-48 h
- IV antibiotics: as appropriate for clinical scenario; consider penicillin 4 million IU IV q4h and clindamycin 900 mg IV q6h until final cultures available (the combination can be synergistic if Group A streptococcus) or vancomycin and clindamycin
- ICU admission and infectious disease consult recommended after urgent surgical debridement by plastic surgery

# Ulcers

## Lower Limb Ulcers

### Traumatic Ulcers (Acute)
- failure of wound to heal, usually due to compromised blood supply and unstable scar, secondary to pressure or bacterial colonization/infection
- usually over bony prominence ± edema ± pigmentation changes ± pain
- treatment: involvement of vascular surgery. Any debridement of ulcer and compromised tissues must be preceded by ABIs and vascular Doppler. Ulcers or compromised tissues left to heal via secondary intention with dressings may need reconstruction with local or distant flap in select cases, vascular status of limb must be assessed clinically and via vascular studies (i.e. ABI, duplex Doppler)

### Non-Traumatic Ulcers (Chronic)

**Table 13. Venous vs. Arterial vs. Diabetic Ulcers**

| Characteristic | Venous (70% of vascular ulcers) | Arterial | Diabetic |
|---|---|---|---|
| **Cause** | Valvular incompetence<br>Venous HTN | 2° to small and/or large vessel disease (be aware of risk factors) | Peripheral neuropathy: decreased sensation<br>Atherosclerosis: microvascular disease |
| **History** | Dependent edema, trauma<br>Rapid onset ± thrombophlebitis, varicosities | Arteriosclerosis, claudication<br>Usually >45 yr<br>Slow progression | DM<br>Peripheral neuropathy<br>Trauma/pressure |
| **Common Distribution** | Medial malleolus ("Gaiter" locations) | Distal locations (e.g. lower limb, feet) | Pressure point distribution (more likely metatarsal heads) |
| **Appearance** | Yellow exudates<br>Granulation tissue<br>Varicose veins<br>Brown discolouration of surrounding skin | Pale/white, necrotic base ± dry eschar covering | Necrotic base |
| **Wound Margins** | Irregular | Even ("punched out") | Irregular or "punched out" or deep |
| **Depth** | Superficial | Deep | Superficial/deep |
| **Surrounding Skin** | Venous stasis discolouration (brown) | Thin, shiny, dry skin; hairless, cool | Thin, dry skin ± hyperkeratotic border<br>Hypersensitive/ischemic |

ABI in diabetics can be falsely normal due to incompressible arteries secondary to plaques/calcification

**Table 13. Venous vs. Arterial vs. Diabetic Ulcers** (continued)

| Characteristic | Venous (70% of vascular ulcers) | Arterial | Diabetic |
|---|---|---|---|
| **Pulses** | Normal distal pulses | Decreased or no distal pulses | Decreased pulses likely (take caution in calcified vessels) |
| **Vascular Exam** | ABI >0.9<br>Doppler; abnormal venous system | ABI <0.9<br>Pallor on elevation, rubor on dependency<br>Delayed venous filling | ABI is inaccurately high (due to PVD)<br>Usually associated with arterial disease (microvascular/ macrovascular disease) |
| **Pain** | Moderately painful<br>Increased with leg dependency, decreased with elevation<br>No rest pain | Extremely painful<br>Decreased with dependency, increased with leg elevation and exercise (claudication)<br>Rest pain | Painless (if neuropathy)<br>No claudication or rest pain<br>Associated paresthesia, anesthesia |
| **Treatment** | Leg elevation, rest<br>Compression at 30 mmHg (stockings or elastic bandages)<br>Moist wound dressings<br>± topical, systemic antibiotics if infected<br>± skin grafts | Rest, no elevation, no compression<br>Moist wound dressing ± topical and/or systemic antibiotics if infected<br>Modify risk factors (smoking, diet, exercise, etc.)<br>Vascular surgical consultation (angioplasty or bypass)<br>Treat underlying conditions (DM, proximal arterial occlusion, etc.) | Control DM<br>Careful wound care<br>Foot care<br>Orthotics, off loading<br>Early intervention for infections (topical and/ or systemic antibiotics if infected)<br>Vascular surgical consultation |

# Pressure Ulcers



### Common Sites
- over bony prominences; 95% on lower body

### Stages of Development
1. hyperemia: disappears 1 h after pressure removed
2. ischemia: follows 2-6 h of pressure
3. necrosis: follows >6 h of pressure
4. ulcer: necrotic area breaks down

### Classification (National Pressure Ulcer Advisory Panel 2014)
- Stage I: non-blanchable erythema present >1 h after pressure relief, skin intact
- Stage II: partial-thickness skin loss
- Stage III: full-thickness skin loss into subcutaneous tissue
- Stage IV: full-thickness skin loss into muscle, bone, tendon, or joint
  - if an eschar is present, must fully debride before staging possible
- Stage X: unstageable ulcer



**A Nutritional Formula Enriched With Arginine, Zinc, And Antioxidants For The Healing Of Pressure Ulcers: A Randomized Trial**
Ann Intern Med 2015;162(3):167-74
Among malnourished patients with pressure ulcers, 8 weeks of supplementation with an oral nutritional formula enriched with arginine, zinc, and antioxidants improves pressure ulcer healing.

### Prevention
- good nursing care (clean dry skin, frequent repositioning), special beds or pressure relief surface, proper nutrition, activity, early identification of individuals at risk (e.g. immobility, incontinence, paraplegia, immunocompromised, DM, etc.)

### Treatment
- depends on individual patient and condition
- 4 main principles:
  - preventative measures (pressure relief, assess for pressure points e.g. wheelchairs; manage continence issues, divert contaminants e.g. urine and feces)
  - treatment of underlying medical issues including nutrition
  - moisture reduction pressure relief
  - wound bed preparation and treatment
- systemic antibiotics for infections
- assess for possible reconstruction

### Complications
- cellulitis, osteomyelitis, sepsis, gangrene

# Burns

## Burn Injuries

### Causal Conditions
- thermal (flame contact, scald)
- chemical
- radiation (UV, medical/therapeutic)
- electrical

### Most Common Etiology
- children: scald burns
- adults: flame burns

**Table 14. Skin Function and Burn Injury**

| Skin Function | Consequence of Burn Injury | Intervention Required |
|---|---|---|
| **Thermoregulation** | Prone to lose body heat | Must keep patient covered and warm |
| **Control of fluid loss** | Loss of large amounts of water and protein from the skin and other body tissues | Adequate fluid resuscitation is imperative |
| **Mechanical barrier to bacterial invasion and immunological organ** | High risk of infection | Antimicrobial dressings (systemic antibiotics if signs of specific infection present)<br>Tetanus prophylaxis if not already administered |

## Pathophysiology of Burn Wounds

- amount of tissue destruction is based on temperature, time of exposure, and specific heat of the causative agent
- zone of hyperemia: vasodilation from inflammation; entirely viable, cells recover within 7 d; contributes to systemic consequences seen with major burns
- zone of stasis (edema): decreased perfusion; microvascular sludging and thrombosis of vessels results in progressive tissue necrosis → cellular death in 24-48 h without proper treatment
  - factors favouring cell survival: moist, aseptic environment, rich blood supply
  - zone where appropriate early intervention has most profound effect in minimizing injury
- zone of coagulation (ischemia): no blood flow to tissue → irreversible cell damage → cellular death/necrosis

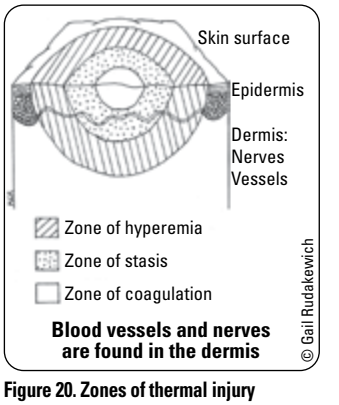



**Figure 20. Zones of thermal injury**

## Diagnosis and Prognosis

- burn size
  - % of TBSA burned: rule of 9s for 2° and 3° burns only (children <10 yr old use Lund-Browder chart)
  - for patchy burns, surface area covered by patient's palm (fingers closed) represents approximately 1% of TBSA
- age: more complications if <3 yr or >60 yr old
- depth: difficult to assess initially – history of etiologic agent and time of exposure helpful (see Table 15)
- location: face and neck, hands, feet, perineum are critical areas requiring special care of a burn unit (see *Indications for Transfer to Burn Centre*, PL20)
- inhalation injury: can severely compromise respiratory system, affect fluid requirement estimation (underestimate), mortality secondary to ARDS
- associated injuries (e.g. fractures)
- comorbid factors (e.g. concurrent disability, alcoholism, seizure disorders, chronic renal failure) can exacerbate extent of injury, other trauma

Prognosis best determined by burn size (TBSA), age of patient, presence/absence of inhalation injury

Circumferential burns can restrict respiratory excursion and/or blood flow to extremities and require escharotomy

TBSA does not include areas with 1° burns

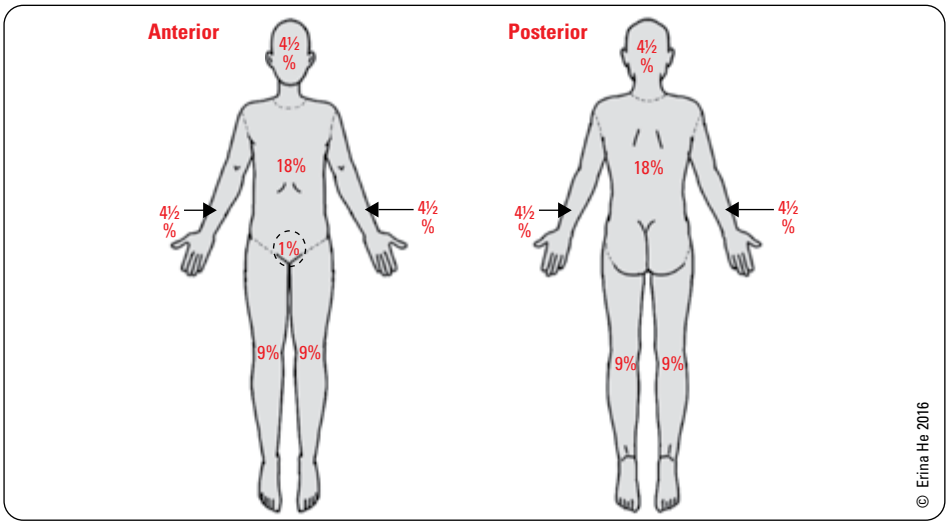
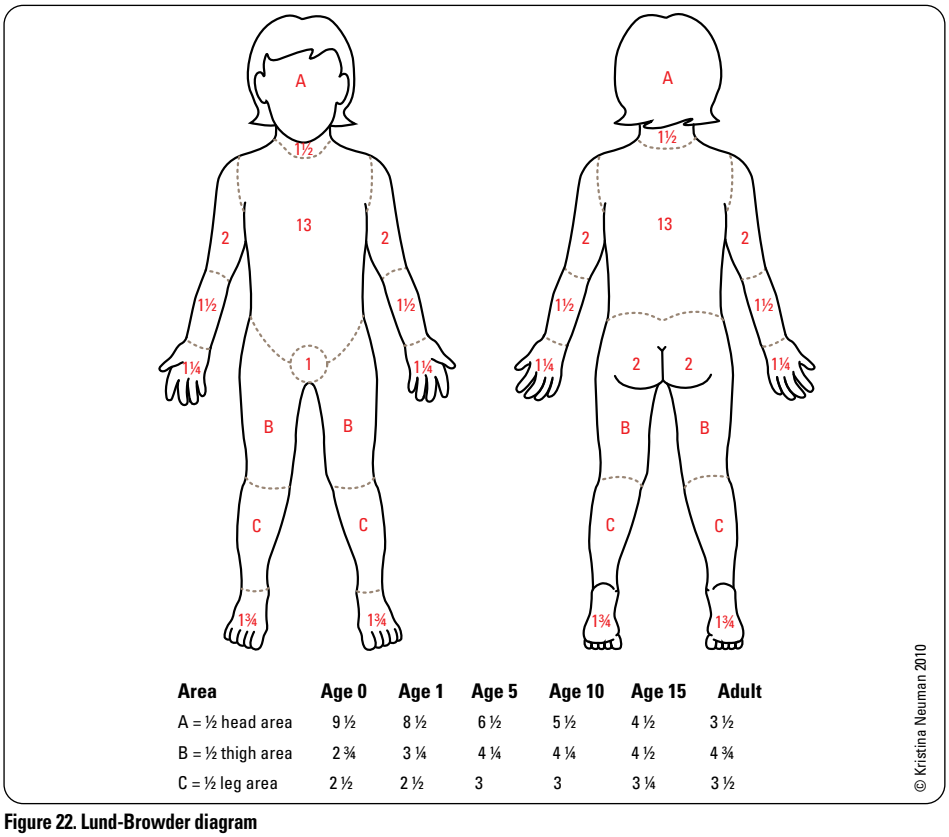



**Figure 21. Rule of 9s for TBSA**




| Area | Age 0 | Age 1 | Age 5 | Age 10 | Age 15 | Adult |
|---|---|---|---|---|---|---|
| A = ½ head area | 9 ½ | 8 ½ | 6 ½ | 5 ½ | 4 ½ | 3 ½ |
| B = ½ thigh area | 2 ¾ | 3 ¼ | 4 ¼ | 4 ¼ | 4 ½ | 4 ¾ |
| C = ½ leg area | 2 ½ | 2 ½ | 3 | 3 | 3 ¼ | 3 ½ |

**Figure 22. Lund-Browder diagram**

**Burn Size And Survival Probability In Pediatric Patients In Modern Burn Care: A Prospective Observational Cohort Study**
Lancet 2012 Mar 17;379(9820):1013-21
**Study**: Single-centre prospective observational cohort study using clinical data for pediatric patients with burns of at least 30% of their total body surface area (TBSA). Patients were stratified by burn size in 10% increments, ranging from 30% to 100% TBSA.
**Results**: 952 severely burned paediatric patients were admitted to the centre between 1998 and 2008. 123 (13%) patients died, 154 (16%) developed multiorgan failure, and 89 (9%) had sepsis. Burn size of 62% TBSA was a crucial threshold for mortality.
**Conclusions**: In a modern pediatric burn care setting, a burn size of roughly 60% TBSA is a crucial threshold for postburn morbidity and mortality. We recommend that pediatric patients with greater than 60% TBSA burns be immediately transferred to a specialised burn centre. Furthermore, patients should be treated with increased vigilance and improved therapies at the burn centre, in view of the increased risk of poor outcome associated with this burn size.

**Table 15. Burn Depth (1st, 2nd, 3rd degree)**

| Nomenclature | Traditional Nomenclature | Depth | Clinical Features |
|---|---|---|---|
| **Erythema/Superficial** | First degree | Epidermis | Painful, sensation intact, erythema, blanchable |
| **Superficial-Partial Thickness** | Second degree | Into superficial dermis | Painful, sensation intact, erythema, blisters with clear fluid, blanchable, hair follicles present |
| **Deep-Partial Thickness** | Second degree | Into deep (reticular) dermis | Insensate, difficult to distinguish from full thickness, does not blanch, some hair follicles still attached, softer than full thickness burn |
| **Full Thickness** | Third degree<br><br>Fourth degree | Through epidermis and dermis<br>Injury to underlying tissue structures (e.g. muscle, bone) | Injury to underlying tissue structures (e.g. muscle, bone) Insensate (nerve endings destroyed), hard leathery eschar that is black, grey, white, or cherry red in colour; hairs do not stay attached, may see thrombosed veins |

# Indications for Transfer to Burn Centre

### American Burn Association Criteria

- patients with partial or full-thickness burns that involve the hands, feet, genitalia, face, eyes, ears, and/or major joints or perineum
- partial thickness burns ≥20% TBSA in patients aged 10-50 yr old
- partial thickness burns ≥10% TBSA in children aged ≤10 or adults aged ≥50 yr old
- full thickness burns ≥5% TBSA in patients of all ages
- electrical burns, including lightning (internal injury underestimated by TBSA), and chemical burns
- inhalation injury (high risk of mortality and may lead to respiratory distress)
- burn injuries in patients with medical comorbidities could complicate management and recovery
- any patient with simultaneous trauma plus burns should be stabilized for trauma first, then triaged appropriately to burn centre
- any patients with burn injury and who will require special emotional, social, and rehabilitation intervention
- children with burns in a hospital not equipped with pediatric care specialists

# Acute Care of Burn Patients

- adhere to ATLS protocol
- resuscitation using Parkland formula to restore plasma volume and cardiac output. Parkland formula is a starting estimate and patients may require more volume. Other formulas exist, but the Parkland formula is predominately used in North America
  - 4 cc/kg x %TBSA (greater than first degree) x wt(kg) (1/2 within first 8 h of sustaining burn, 1/2 in next 16 h)
- extra fluid administration required if:
  - burn >80% TBSA
  - 4° burns
  - associated traumatic injury
  - electrical burn
  - inhalation injury
  - delayed start of resuscitation
  - pediatric burns
- monitor resuscitation
  - urine output is best measure: maintain at >0.5 cc/kg/h (adults) and 1.0 cc/kg/h in children <12 yr
  - maintain a clear sensorium, HR <120/min, MAP >70 mmHg
- burn-specific care
  - relieve respiratory distress: intubation and/or escharotomy
  - escharotomy in circumferential extremity burn, including digits
  - prevent and/or treat burn shock: 2 large bore IVs for fluid resuscitation
  - insert Foley catheter to monitor urine output
  - identify and treat immediate life-threatening conditions (e.g. inhalation injury, CO poisoning)
  - determine TBSA affected first, since depth is difficult to determine initially (easier to determine after 24 h)
- tetanus prophylaxis if needed
  - all patients with burns >10% TBSA, or deeper than superficial-partial thickness, need 0.5 cc tetanus toxoid
  - also give 250 U of tetanus Ig if prior immunization is absent/unclear, or the last booster >10 yr ago
- baseline laboratory studies (Hb, U/A, BUN, CXR, electrolytes, Cr, glucose, CK, ECG, cross-match if traumatic injury, ABG, carboxyhemoglobin)
- cleanse, debride, and treat the burn injury (antimicrobial dressings)
- early excision and grafting important for outcome

### Respiratory Problems

- 3 major causes
  - burn eschar encircling chest
    - distress may be apparent immediately
    - perform escharotomy to relieve constriction
  - CO poisoning
    - may present immediately or later
    - treat with 100% $O_2$ by facemask (decreases half-life of carboxyhemoglobin from 210 to 59 min) until carboxyHb <10%
  - smoke inhalation leading to pulmonary injury
    - chemical injury to alveolar basement membrane and pulmonary edema (insidious onset)
    - risk of pulmonary insufficiency (up to 48 h) and pulmonary edema (48-72 h)
    - watch for secondary bronchopneumonia (3-25 d) leading to progressive pulmonary insufficiency
    - intubate patient with any signs of inhalation injuries



**Inhalation Injuries 101**

**Indicators of Inhalation Injury**

- Injury in a closed space
- Facial burn
- Singed nasal hair/eyebrows
- Soot around nares/oral cavity
- Hoarseness
- Conjunctivitis
- Tachypnea
- Carbon particles in sputum
- Elevated blood CO levels (i.e. brighter red)
- Suspected inhalation injury requires immediate intubation due to impending airway edema; failure to diagnose inhalation injury can result in airway swelling and obstruction, which, if untreated, can lead to death
- Neither CXR or ABG can be used to rule out inhalation injury
- Direct bronchoscopy now used for diagnosis
- Signs of CO poisoning (headache, confusion, coma, arrhythmias)

## Burn Wound Healing

### Table 16. Burn Shock Resuscitation (Parkland Formula)

| | |
|---|---|
| **Hour 0-24** | 4 cc RL/kg/% TBSA with 1/2 of total in first 8 h from time of injury and 1/2 of total in next 16 h from time of injury |
| **Hour 24-30** | 0.35-0.5 cc plasma/kg/%TBSA |
| **>Hour 30** | D5W at rate to maintain normal serum sodium |

*Do not forget to add maintenance fluid to resuscitation

### Table 17. Burn Wound Healing

| Depth | Healing |
|---|---|
| **First degree** | No scarring; complete healing |
| **Second degree (Superficial partial)** | Spontaneously re-epithelialize in 7-14 d from retained epidermal structures<br>± residual skin discolouration<br>Hypertrophic scarring uncommon; grafting rarely required |
| **Deep second degree (Deep partial)** | Re-epithelialize in 14-35 d from retained epidermal structures<br>Hypertrophic scarring frequent<br>Grafting recommended to expedite healing |
| **Third degree (Full thickness)** | Re-epithelialize from the wound edge<br>Grafting/flap necessary to replace dermal integrity, limit hypertrophic scarring |
| **Fourth degree** | Often results in amputations<br>If not requiring amputation, needs flap for coverage after debridement (do not re-epithelialize, cannot graft) |

## Treatment

- 3 stages
  1. assessment: depth determined
  2. management: specific to depth of burn and associated injuries
  3. rehabilitation
- first degree
  - treatment aimed at comfort
  - topical creams (pain control, keep skin moist) ± aloe
  - oral NSAIDs (pain control)
- superficial second degree/partial thickness
  - daily dressing changes with topical antimicrobials (such as Polysporin®); leave blisters intact unless circulation impaired or over joint and inhibiting motion
- deep second degree/deep partial thickness and third degree/full thickness
  - prevent infection and sepsis (significant complication and cause of death in patients with burns)
    - most common organisms: *S. aureus, P. aeruginosa,* and *C. albicans*
      - day 1-3 (rare): Gram-positive
      - day 3-5: Gram-negative (*Proteus, Klebsiella*)
    - topical antimicrobials: treat colonized wounds (from skin flora, gut flora, or caregiver)
  - remove dead tissue
- surgically debride necrotic tissue, excise to viable (bleeding) tissue

**Risk Factors for Infection of Burn Wounds**

**Patient Related**
- Extent >30% TBSA
- Depth: full-thickness and deep partial-thickness
- Patient age (higher risk with very young and very old)
- Comorbidities
- Wound dryness
- Wound temperature
- Secondary impairment of blood flow to wound
- Acidosis

**Microbial Factors**
- Density >$10^5$ organisms per gram of tissue
- Motility
- Virulence and metabolic products (endotoxin, exotoxin, permeability factors, other factors)
- Antimicrobial resistance

### Table 18. Antimicrobial Dressings for Burns

| Antibiotic | Pain with Application | Penetration | Adverse Effects |
|---|---|---|---|
| **Silver nitrate** (0.5% solution) | None | Minimal | May cause methemoglobinemia, stains (black), leaches sodium from wounds |
| **Nanocrystalline silver-coated dressing** (Acticoat®) | None or transient | Medium, does not penetrate eschar | May stain, producing a pseudoeschar or facial discolouration (argyria-like symptoms); raised liver enzymes |
| **Silver sulfadiazine** (cream) (Flamazine®, Silvadene®) | Minimal | Medium, penetrates eschar poorly | Slowed healing, leukopenia, mild inhibition of epithelialization |
| (Sulfamylon®) | Moderate | Well, penetrates eschar; commonly used on ears for deep burns | Mild inhibition of epithelialization, may cause metabolic acidosis with wide application |

- early excision and grafting is the mainstay of treatment for deep/full thickness burns
- initial dressing should decrease bacterial proliferation
- prevention of wound contractures: pressure dressings, joint splints, early physiotherapy

### Other Considerations in Burn Management

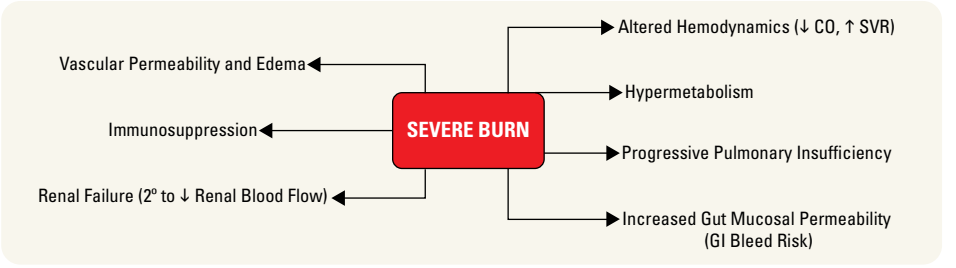



**Figure 23. Systemic effects of severe burns**

- nutrition
  - hypermetabolism: TBSA >40% have BMR 2-2.5x predicted
  - consider nutritional supplementation e.g. calories, vitamin C, vitamin A, $Ca^{2+}$, $Zn^{2+}$, $Fe^{2+}$
- immunosuppression and sepsis
  - must keep bacterial count $<10^5$ bacteria/g of tissue (blood culture may not be positive)
  - signs of sepsis: sudden onset of hyper/hypothermia, unexpected CHF or pulmonary edema, development of ARDS, ileus >48 h post-burn, mental status changes, azotemia, thrombocytopenia, hypofibrinogenemia, hyper/hypoglycemia (especially if burn >40% TBSA)
- GI bleed may occur with burns >40% TBSA (usually subclinical)
  - treatment: tube feeding or NPO if there is a GI bleed, antacids, H2 blockers (preventative)
- renal failure secondary to under resuscitation, drugs, myoglobin, etc.
- progressive pulmonary insufficiency
  - can occur after: smoke inhalation, pneumonia, cardiac decompensation, sepsis
- wound contracture and hypertrophic scarring (outcomes optimized with timely wound closure, splinting, pressure garments) and physiotherapy

# Special Considerations

## CHEMICAL

- major categories: acid burns, alkaline burns, phosphorous burns, chemical injection injuries
- common agents: cement, hydrofluoric acid, phenol, tar
- mechanism of injury: chemical solutions coagulate tissue protein leading to necrosis
  - acids → coagulation necrosis
  - alkalines → saponification followed by liquefactive necrosis
- severity related to: type of chemical (alkali worse than acid), temperature, volume, concentration, contact time, site affected, mechanism of chemical action, degree of tissue penetration
- burns are deeper than they initially appear and may progress with time

### Treatment (General)

- ABCs, monitoring
- remove contaminated clothing and brush off any dry powders before irrigation
- irrigation with water for 1-2 h under low pressure (contraindicated in heavy metal burns, such as sodium, potassium, magnesium, and lithium; in these cases, soak in mineral oil instead)
- inspect eyes, if affected: wash with saline and refer to ophthalmology
- inspect nails, hair, and webspaces
- correct metabolic abnormalities and tetanus prophylaxis if necessary
- contact poison control line if necessary
- local wound care 12 h after initial dilution (debridement)
- wound closure same as for thermal burn
- beware of underestimated fluid resuscitation, renal, liver, and pulmonary damage

**Table 19. Special Burns and Treatments**

| | |
|---|---|
| **Acid Burn** | Water irrigation, followed by dilute solution of sodium bicarbonate |
| **Hydrofluoric Acid** | Water irrigation; clip fingernails to avoid acid trapping; topical calcium gel ± subcutaneous injection of calcium gluconate ± 10% calcium gluconate IV depending on amount of exposure and pain |
| **Sulfuric Acid** | Treat with soap/lime prior to irrigation as direct water exposure produces extreme heat |
| **Tar** | Remove with repeated application of petroleum-based antibiotic ointments (e.g. Polysporin®) |

## ELECTRICAL BURNS

- depth of burn depends on voltage and resistance of the tissue (injury more severe in tissues with high resistance)
- often presents as small punctate burns on skin, with extensive deep tissue damage which requires debridement
- electrical burns require ongoing monitoring, as latent injuries can occur
- watch for system-specific damages and abnormalities
  - abdominal: intraperitoneal damage
  - bone: fractures and dislocations especially of the spine and shoulder
  - cardiopulmonary: anoxia, ventricular fibrillation, arrhythmias
  - muscle: myoglobinuria indicates significant muscle damage → compartment syndrome
  - neurological: seizures and spinal cord damage
  - ophthalmology: cataract formation (late complication)
  - renal: acute tubular necrosis resulting from toxic levels of myoglobin and hemoglobin
  - vascular: vessel thrombosis → tissue necrosis (increased Cr, $K^+$, and acidity), decrease in RBC (beware of hemorrhages/delayed vessel rupture)

**Tissue Resistance to Electrical Current**
nerve < vessel/blood < muscle < skin < tendon < fat < bone

### Treatment

- ABCs, primary and secondary survey, treat associated injuries
- beware of cardiac arrhythmias (continue cardiac monitoring)
- monitor: hemochromogenuria, compartment syndrome, urine output
- wound management: topical agent with good penetrating ability (silver sulfadiazine or mafenide acetate)
- debride nonviable tissue early and repeat prn (every 48 h) to prevent sepsis
- amputations frequently required

## FROSTBITE

- see Emergency Medicine, ER46

# Hand

## Traumatic Hand

**Table 20. Key Features of the History and Physical Exam of the Injured Hand**

| | | |
|---|---|---|
| **HISTORY** | | |
| **Key Questions** | Age | Tetanus status |
| | Hand dominance | Diabetes |
| | Occupation | Smoking status |
| | Time and place of accident | Last oral intake |
| | Mechanism of injury | |
| | Initial treatment received | |
| **PHYSICAL EXAM** | | |
| **Observation** | Position of finger | Abnormal cascade (fingers normally slightly flexed and point towards scaphoid), scissoring |
| | Deformity | Bony protrusions or specific deformities (e.g. mallet, boutonnière, and swan neck deformity) |
| | Bruising or swelling | May indicate underlying skeletal injury |
| | Sweating pattern (usually felt more so than from observation) | May indicate denervation |
| | Anatomical structures beneath | If open laceration, need to explore within wound (under sterile conditions) |
| | **Structure** | **Examination** |
| **Vascular Status** | Radial and ulnar arteries | Palpate pulses<br>Allen's test |
| | Digital arteries | Assess capillary refill (<2-3 s)<br>Doppler ultrasound |
| | Temperature and skin turgor | For each test, need to compare both sides |
| **Sensory** (see Figure 4) | Median nerve | Volar radial tip of index finger |
| | Ulnar nerve | Volar ulnar tip of little finger |
| | Radial nerve | Dorsal web space of the thumb |
| | Digital nerves | 2 point discrimination on both the radial and ulnar side of the DIP creases (static or moving 2 point discrimination) |

**Compartment Syndrome**
Watch out for these signs with a closed or open injury: tense, painful extremity (worse on passive stretch), parasthesia/paralysis, pallor, distal pulselessness (often late in process), and contracture (irreversible ischemia).
Intracompartmental pressures can be measured (normal pressure = up to 12 mmHg, abnormal is 30-40 mmHg), but a clinical diagnosis is an indication for an emergent fasciotomy; if untreated, end result is ischemic contracture of the extremity (Volkmann's contracture).

**Approach to Hand Lacerations**

**TIN AX**
**T**etanus prophylaxis
**I**rrigate with NS (copious irrigation and debridement in a timely manner)
**N**PO (NPO if you are considering replanting or an urgent OR, otherwise most operations are done as elective procedures)
**A**ntibiotic prophylaxis (controversial – most require no antibiotics, mainly needed for animal bites and dirty wounds)
**X**-rays

**Allen's Test**: You need to exsanguinate the hand by having the patient open and close the hand. Then, while patient's hand is firmly closed, occlude both radial and ulnar arteries. Once fist is open, release either artery and assess collateral flow

**Table 20. Key Features of the History and Physical Exam of the Injured Hand** (continued)

| | Structure | Examination |
|---|---|---|
| **Motor Function** | Median nerve | Flex DIP of index finger (to test the anterior interosseus nerve (AIN) branch) |
| | | Touch the tip of the index finger to the thumb trying to break through ("OK sign") (to test the AIN branch) |
| | | Thumb to ceiling with palm up (to test the recurrent motor branch) |
| | | Thumb to tip of 5th digit (to test the recurrent motor branch) |
| | Ulnar nerve | Extrinsic muscles: flex DIP of little finger |
| | | Intrinsic muscles: abduct index finger ("Peace sign") or patient able to hold piece of paper between adducted thumb and index finger and resist pulling ("Froment's sign") |
| | Radial nerve | Extrinsic muscles: extend thumb ("thumb's up") and wrist |
| **Range of Motion** | Tendons, bones, joints, nerves | Assess active and passive range of motion of wrist: extension/flexion/ulnar/radial deviation; finger abduction/adduction/flexion/extension, thumb flexion/extension/abduction/adduction/opposition |
| **Tendons** | FDP | Stabilize PIP in extension, ask patient to flex fingers (at DIP) |
| | FDS | Stabilize non-exam fingers in extension (neutralizes FDP) and ask patient to flex examination finger (at PIP) |
| **Palpation** | Bones | Focal tenderness or abnormal alignment |
| | Joints | Instability may indicate ligamentous injury or dislocation |

# General Management of Hand Injuries

## Nerves

- **test the nerve function BEFORE putting in local anesthesia**
- primary repair for a clean injury within 2 wk and without concurrent major injuries; secondary repair if >2 wk (may require nerve graft)
- epineurial repair of all digital nerves with minimal tension
- post-operative: dress wound, elevate hand, and immobilize
- Tinel's sign (cutaneous percussion over the repaired nerve) produces paresthesias and defines level of nerve regeneration
  - Wallerian degeneration occurs in the first 2 wk, which is why there is no Tinel's sign until after this time period
  - a peripheral nerve regenerates at 1 mm/d
  - paresthesias felt at area of percussion because regrowth of myelin (Schwann cells) is slower than axonal regrowth → percussion on exposed free-end of axon generates paresthesia

## Vessels

- often associated with nerve injury (anatomical proximity)
- control bleeding with direct pressure and hand elevation
- if digit devascularized, optimal repair within 6 h
- close skin, then dress, immobilize, and splint hand with fingertips visible
- monitor colour, capillary refill, skin turgor, fingertip temperature post-revascularization

**Hand Exam**

- Never blindly clamp a bleeding vessel as nerves are often found in close association with vessels
- Never explore any volar hand wound in the ER
- Arterial bleeding from a volar digital laceration is likely associated with a nerve laceration (nerves in digits are superficial to arteries)

## Tendons

- most tendon lacerations require primary repair
- many extensors are repaired in the emergency room, flexors are repaired in the operating room within 1 wk (but 2 wk may still be considered)
- avoid excessive immobilization after repair (specific protocols for flexors to minimize stiffness and facilitate rehabilitation)

## Bones

- see *Fractures and Dislocations*, PL27

## Nailbed

- subungual hematomas >50% of the nail surface area need to be drained (trephination), done under a digital block by puncturing nail plate
- if suspecting greater severity of injury (e.g. distal phalanx displaced fracture, laceration of nail bed), remove nail plate to examine underlying nailbed under digital block anesthesia
- irrigate wound and nail thoroughly
- suture repair of nailbed with chromic suture
- replace cleaned nail, which acts as a splint for any underlying distal phalangeal fracture and prevents adhesion formation between nail fold and nailbed

# Hand Infections

## Principles

- trauma is most common cause
- 5 cardinal signs: rubor (red), calor (hot), tumour (swollen), dolor (painful), and functio laesa (loss of function)
- 90% caused by Gram-positive organisms
- most common organisms (in order) – *S. aureus, S. viridans,* Group A Streptococcus*, S. epidermidis*, and *Bacteroides melaninogenicus* (MRSA is becoming more common)

## TYPES OF INFECTIONS

### Deep Space Infections

- abscess formation in deep spaces of the hand, most commonly thenar or mid-palm space
- uncommon, there are 9 spaces in the hand

### Felon

- **definition**: abscess in the pulp of a fingertip or thumb that occurs following a puncture wound into the pad of the digit; may be associated with osteomyelitis (akin to compartment syndrome and can lead to skin necrosis)
- **treatment**: elevation, warm soaks, cloxacillin 500 mg PO q6h (if in early stage); if obvious abscess or pressure on the overlying skin or failure to resolve with conservative measures, then needs I&D, take cultures/Gram stain and adjust antibiotics to culture results

### Flexor Tendon Sheath Infection

- *Staphylococcus* > *Streptococcus* > Gram-negative rods
- **definition**: abscess within the flexor tendon sheath (flexor tenosynovitis), commonly caused by a penetrating injury and can lead to tendon necrosis and rupture if not treated; it is often suppurative; however, there can be very little pus early on
- **clinical features**: Kanavel's 4 cardinal signs
  1. point tenderness along flexor tendon sheath
  2. severe pain on passive extension of digit
  3. fusiform swelling of entire digit
  4. flexed posture (increased comfort)
- **treatment**
  - non-suppurative: IV antibiotics, resting hand splint and elevation until infection resolves, aggressive hand therapy after
  - suppurative (produces pus): I&D in OR (catheter irrigation is no longer performed because it causes maceration)

### Herpetic Whitlow

- HSV-1, HSV-2
- **definition**: painful vesicle(s) around fingertip or thumb
  - often found in medical/dental personnel and children
- **clinical features**: can be associated with fever, malaise and lymphadenopathy, prodromal phase
  - patient is infectious until lesion has completely healed
- **treatment**: diagnosed clinically, if in doubt confirm with viral culture/PCR or Tzanck smear, usually self-limited, consider oral acyclovir in severe cases; I&D is contraindicated

### Paronychia

- acute = *Staphylococcus*; chronic = *Candida*
- **definition**: infection (granulation tissue) of soft tissue around fingernail (within the paronychium and/or beneath eponychial fold)
- **etiololgy**
  - acute paronychia: a "hangnail", artificial nails, and nail biting
  - chronic paronychia: prolonged exposure to moisture
- **treatment**
  - acute paronychia: warm compresses and oral antibiotics if caught early; if abscess present, drainage with blade (avoid hitting nail bed) and oral/IV antibiotics; if abscess extends to below nail plate, nail plate removal may be required
  - chronic paronychia: anti-fungals, eponychial marsupialization, nail plate removal may be required

# Amputations

## Hand or Finger

- emergency management: injured patient and amputated part requires attention
  - patient: x-rays (stump and amputated part), NPO, clean wound and irrigate with NS, dress stump with nonadherent dressing, cover with dry sterile dressing, tetanus and antibiotic prophylaxis (cephalosporin/erythromycin)
  - **amputated part**: x-rays, gently irrigate with RL, wrap amputated part in a NS/RL soaked sterile gauze and place inside waterproof plastic bag, place in a container, then place container on ice
- **indications for replantation**
  - **age**: children often better results than adults
  - **level of injury**: thumb and multiple digit amputations are higher priority; multiple level amputation is a contraindication to replant
  - **nature of injury**: clean cut injuries have greater success; avulsion and crush injuries are relative contraindications to replant
- if replant contraindicated, manage stump with revision amputation
  - involves debriding stump of wound, trimming back the bone and nerve endings, and gently closing the skin
  - commonly done in the ER under digital block

# Tendons

## Common Extensor Tendon Deformities

**Table 21. Extensor Tendon Deformities**

| Injury | Definition | Zone | Etiology/Clinical Features | Treatment |
|---|---|---|---|---|
| **Mallet Finger** | DIP flexed with loss of active extension | 1 | There are bony and non-bony mallets<br>Bony: Fracture of distal phalanx distal to tendon insertion<br>Non-bony: Forced flexion of the extended DIP leading to extensor tendon rupture at DIP (e.g. sudden blow to tip of the finger) | Splint DIP in extension for 6 wk, followed by 2 wk of night splinting; if inadequate improvement after 6 wk, check splinting routine and recommend 4 more wk of continuous splinting |
| **Boutonnière Deformity** | PIP flexed, DIP hyperextended | 3 | Injury or disease affecting the extensor tendon insertion into the dorsal base of the middle phalanx<br>Associated with RA or trauma (laceration, volar dislocation, acute forceful flexion of PIP) | Splint PIP in extension and allow active DIP motion |
| **Swan Neck Deformity** | PIP hyperextended, DIP flexed | 1,3 | Trauma (PIP volar plate injury)<br>Associated with RA and old, untreated mallet deformity<br>Splint to prevent PIP hyperextension or DIP flexion | Corrective procedures involve tendon rebalancing or arthrodesis/ arthroplasty |

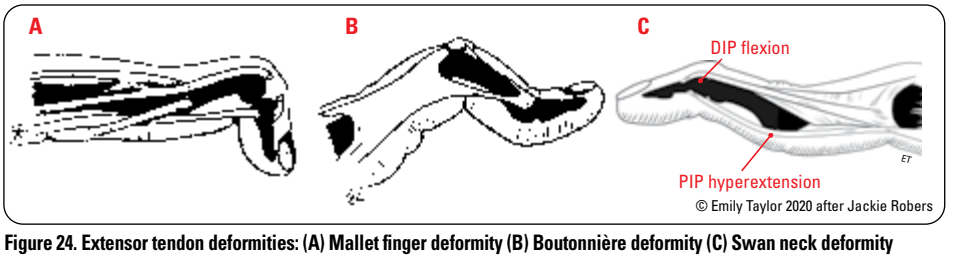



**Figure 24. Extensor tendon deformities: (A) Mallet finger deformity (B) Boutonnière deformity (C) Swan neck deformity**

## De Quervain's Tenosynovitis

- **definition**: tenosynovitis is inflammation of the tendon and/or its sheath. Most common is De Quervain's tenosynovitis (inflammation of the extensor tendons in the 1st dorsal compartment [APL and EPB])
- **clinical features**
  - +ve Finkelstein's test (pain over the radial styloid induced by making fist, with thumb in palm, and ulnar deviation of wrist)
  - pain localized to the 1st extensor compartment
  - tenderness and crepitation over radial styloid may be present
  - differentiate from CMC joint arthritis (CMC joint arthritis will have a positive grind test, whereby crepitus and pain are elicited by axial pressure to the thumb)
- **treatment**
  - mild: NSAIDs, splinting, and steroid injection into the tendon sheath (successful in over 60% of cases)
  - severe: surgery to open 1st dorsal compartment and release stenotic tendon sheaths of APL and EPB

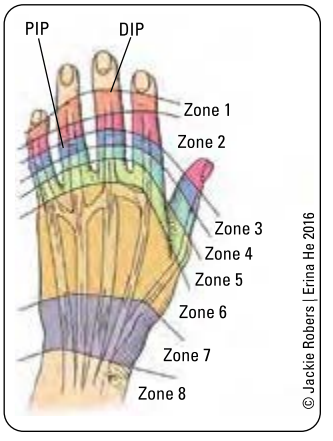



**Figure 25. Zone of extensor tendon injury** (odd numbered zones fall over a joint)

### Ganglion Cyst
- **definition**
  - fluid-filled synovial lining that protrudes between carpal bones or from a tendon sheath; most commonly carpal in origin
  - most common soft tissue tumour of hand and wrist (60% of masses)
- **clinical features**
  - most commonly on the dorsal wrist overlying the scapholunate ligament, followed by the volar surface of the wrist overlying the radioscaphoid or scaphotrapezial joints
  - 3 times more common in women than in men
  - more common in younger individuals (2nd to 4th decades)
  - can be large or small – may drain internally so size may wax and wane
  - often non-tender, although tenderness increased when cyst is smaller (from increased pressure within smaller cyst sac)
- **treatment**
  - conservative treatment: do nothing
  - aspiration (recurrence rate 30-60%)
  - steroid injection if painful (done in combination with aspiration, as results alone are no better than aspiration)
  - consider operative excision of cyst and stalk (recurrence rate 5.9% for dorsal wrist ganglion, 30% for volar)

### Common Flexor Tendon Deformities
- flexor tendon zones (important for prognosis of tendon lacerations)
- "no-man's land" (zone 2) (see Figure 26)
  - between distal palmar crease and mid-middle phalanx
  - zone where superficialis and profundus lie ensheathed together
  - recovery of glide very difficult after injury

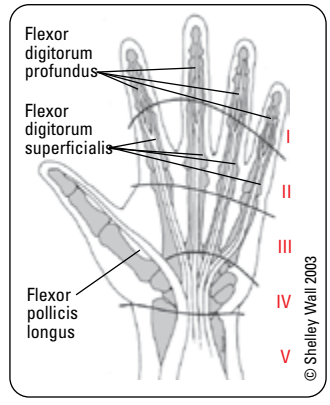


**Figure 26. Zones of the flexor tendons**

### Stenosing Tenosynovitis (trigger finger/thumb)
- **definition**: inflammation and thickening of tendon or tendon sheath/pulley (most commonly at A-1 pulley near MCP), preventing smooth gliding of tendon through the sheath/pulley and resulting in locking of thumb or finger in flexion/extension
- **etiology**: idiopathic or associated with RA, DM, hypothyroidism, gout, and pregnancy
- **clinical features**
  - ring finger is most commonly affected, then long finger and thumb
  - patient complains of catching, snapping, or locking of affected finger
  - tenderness to palpation/nodule at palmar aspect of MCP over A-1 pulley
  - women are 4 times more likely to be affected than men
- **non-surgical treatment**
  - NSAIDs
  - steroid injection; injections less likely to be successful in patients >60 yr, or symptoms greater than 6 mo
  - splint
- **surgical treatment**
  - indicated if no relief of symptoms or minimal relief with steroids
  - incise A-1 flexor pulley to permit unrestricted, full active finger motion


A-2 and A-4 pulleys are most important for function; prevent bowstringing of tendons

## Fractures and Dislocations
- for fracture principles, see Orthopedic Surgery, OR5

### FRACTURES
- about 90% of hand fractures are stable in flexion (splint to prevent extension)
- **position of safety**
  - wrist extension 0-30°
  - MCP flexion 70-90°
  - IP full extension
  - this is done if you want to immobilize a fracture but are not sure whether there are other injuries
- stiffness secondary to immobilization is the most important complication

### Distal Phalanx Fractures
- most commonly fractured bone in the hand
- usual mechanism is crush injury, and thus accompanied by soft tissue injury
- subungual hematoma is common and must be decompressed, especially if there is involvement of >50% of the nail surface area
  - injury involving >50% of the nail surface area often suggests a nail bed laceration, in which the patient would benefit from nail plate removal and nailbed repair surgery
- **treatment**: 3 wk of digital splinting (immobilize the DIP with a STAX™ splint); if intra-articular fracture displaced >30%, then percutaneous pinning (K-wires) and splint

### Proximal and Middle Phalanx Fractures
- check for: rotation, scissoring (overlap of fingers on making a fist), shortening of digit
- non-displaced or minimally displaced: closed reduction (if extra-articular), buddy tape to neighbouring stable digit, elevate hand, motion in guarded fashion early, splinted for 2-3 wk
- displaced, non-reducible, not stable with closed reduction, or rotational or scissoring deformity: percutaneous pinning (K-wires) or ORIF, and splint

### Metacarpal Fractures
- generally accept varying degrees of deviation before reduction required: up to 10° (D2), 20° (D3), 30° (D4), or 40° (D5)
- **Boxer's fracture**: acute angulation of the neck of the 5th metacarpal into palm
  - mechanism: blow on the distal-dorsal aspect of closed fist
  - loss of prominence of metacarpal head, volar displacement of head
  - up to 30-40° angulation may be acceptable
  - if greater angulation, closed reduction should be considered to decrease the angle
  - if stable, ulnar gutter splint for 4-6 wk
- **Bennett's fracture**: two-piece fracture/dislocation of the base of the thumb metacarpal, usually intra-articular
  - unstable fracture
  - APL pulls MC shaft proximally and radially, causing adduction of thumb
  - treat with percutaneous pinning or ORIF, followed by thumb spica for 6 wk
- **Rolando fracture**: T- or Y-shaped fracture of the base of the thumb metacarpal
  - treated like a Bennett's fracture

## DISLOCATIONS
- **treatment**: must be reduced as soon as possible
- dislocation vs. subluxation
  - dislocation: severe injury where articular surfaces of a joint are no longer in contact with one another
  - subluxation: articular surfaces of a joint are partially out of place (i.e. "partial dislocation" – often unstable and requires reduction)

### PIP and DIP Dislocations (PIP more common than DIP)
- usually dorsal dislocation (commonly from hyperextension)
- if closed dislocation: closed reduction and splinting in position of function for 1 wk or buddy taping, and early mobilization (prolonged immobilization causes stiffness)
- open injuries are treated with wound care, irrigation, and debridement, followed by closed or open reduction and antibiotics

### MCP Dislocations (relatively rare)
- dorsal dislocations much more common than volar dislocations
- dorsal dislocation of proximal phalanx on metacarpal head; most commonly index finger (hyperextension)
- two types of dorsal dislocation
  - simple (reducible with manipulation): treat with closed reduction and splinting for 2-4 wk at 60-70° MCP flexion
  - complex (irreducible - most commonly due to volar plate blocking the reduction): treat with open reduction

### Ulnar Collateral Ligament (UCL) Injury
- forced abduction of thumb (e.g. ski pole injury)
- **Skier's thumb**: acute UCL injury – if stable, treated with splint x 6-8 wk; if unstable, patient may have Stener lesion
- **Gamekeeper's thumb**: chronic UCL injury, often requires open repair and tendon graft for stabilization
- **Stener lesion**: the distal portion of the UCL can detach and flip superficial to the adductor aponeurosis and will not appropriately heal – requires open repair
- **evaluation**: radially deviate thumb MCP joint in full extension and at 30° flexion and compare with non-injured hand. UCL rupture is presumed if injured side deviates more than 30° in full extension or more than 15° in flexion

# Dupuytren's Disease

### Definition
- proliferative disorder of the palmar fascia, forming nodules (usually painless), fibrous cords, and flexion contractures at the MCP and interphalangeal joints
- flexor tendons not involved
- Dupuytren's diathesis: male sex, early age of onset, strong family history (autosomal dominant inheritance), involvement of multiple digits, bilateral involvement, and involvement of sites other than palmar aspect of hand, including the plantar fascia (Ledderhose's) and the penis (Peyronie's) – (see Urology, U32)

### Epidemiology
- unusual in patients from African and Asian countries, high incidence in northern Europeans, men > women, often presents in 5th-7th decade of life; associated with but not caused by alcohol use, smoking, and DM

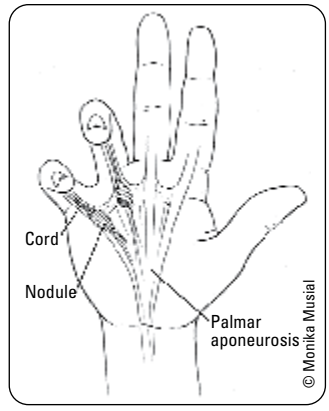


**Figure 27. Dupuytren's disease**

### Clinical Features
- nodules, cords, and contractures of MCP, PIP, and DIP
- order of digit involvement (most common to least common): ring > little > long > thumb > index
- risk of recurrence

### Treatment
- palmar pit or nodule: no surgery (steroid injections for pain)
- palpable band/cord with no limitation of extension (i.e. no contracture) of either MCP or PIP: no surgery
- MCP contracture >30° or PIP contracture of any degree: needle aponeurotomy, collagenase clostridium histolyticum (Xiaflex®) injection, or surgical fasciectomy
- contractures impeding function and/or hygiene: needle aponeurotomy, collagenase injection, or surgical fasciectomy
- MCP joints have better outcomes than PIP joints post-treatment (achievement of near full extension, lower risk of recurrence)

# Carpal Tunnel Syndrome

### Definition
- median nerve compression at the level of the flexor retinaculum/transverse carpal ligament

### Etiology
- median nerve entrapment at wrist
- primary cause is idiopathic
- secondary causes: space occupying lesions (tumours, hypertrophic synovial tissue, fracture callus, and osteophytes); metabolic and physiological (pregnancy, hypothyroidism, acromegaly, and RA); job/hobby related repetitive trauma, especially forced wrist flexion

### Epidemiology
- female:male = 4:1, most common entrapment neuropathy

### Clinical Features
- classically, patient awakened at night with numb/painful hand, relieved by shaking/dangling/rubbing
- on exam, sensory loss in median nerve distribution (see Figure 4), but thenar eminence sensory loss is spared (palmar cutaneous branch given off prior to carpal tunnel)
- decreased light touch and 2-point discrimination at DIP radial and ulnar creases; discriminative touch often lost first
- advanced cases: thenar wasting/weakness due to involvement of the motor branch of the nerve
- ± Tinel's sign (tingling sensation on percussion of nerve)
- ± Phalen's sign (wrist flexion induces symptoms)

### Investigations
- generally a clinical diagnosis
- NCV and EMG studies may be used to objectively confirm the diagnosis if clinical history is atypical

### Treatment
- avoid repetitive wrist and hand motion, wrist splints at night and when repetitive wrist motion required
- conservative: night-time splinting to keep wrist in neutral position
- medical: NSAIDs, local corticosteroids injection (relief from local corticosteroid injections is also diagnostic)
- surgical decompression: transverse carpal ligament incision to decompress median nerve
- indications for surgery: persistent signs and symptoms of median nerve compression not relieved by conservative management or if motor function is compromised

# Brachial Plexus

## Etiology
- common causes of brachial plexus injury: complication of childbirth and trauma
- other causes of injury: compression from tumours, ectopic ribs

## Common Palsies

**Table 22. Named Neonatal Palsies of the Brachial Plexus**

| Palsy | Location of Injury | Mechanism of Injury | Features |
|---|---|---|---|
| **Duchenne-Erb Palsy** | Upper brachial plexus (C5-C6) | Head/shoulder distraction (e.g. motorcycle) | "Waiter's tip deformity" (shoulder internal rotation, elbow extension and pronation, wrist flexion) |
| **Klumpke's Palsy** | Lower brachial plexus (C7-T1) | Traction on abducted arm | "Claw hand"<br>May include Horner's syndrome |

## Differential Diagnosis of Adult-Acquired Brachial Plexus Palsies
- trauma (blunt, penetrating)
- thoracic outlet syndrome
  - associated with large cervical rib, anomalous first rib, strenuous arm work, neck muscle hypertrophy
  - neurogenic: compression of brachial plexus, resulting in upper limb paresthesia, pain, and weakness
  - vascular: compression/thrombosis of subclavian artery/vein, resulting in pain; pallor and Raynaud's if arterial; swelling and cyanosis if venous
- tumour
  - schwannoma: well-defined margins enable total resection
  - neurofibromas: associated with neurofibromatosis type I
  - other: e.g. Pancoast syndrome (apical lung tumour)
- neuropathy (compressive, post-irradiation, viral, diabetic, idiopathic)

## Investigations
- EMG
- MRI: gold standard for identifying soft tissue masses and nerve roots
- CT myelogram: may be more accessible as an alternative to MRI
- closed injuries: if avulsion suspected, then CT myelogram or MRI initially; otherwise, EMG/NCS 12 wk post-injury to assess healing progress
- open injuries: OR for exploration within a few days post-injury (once patient stable)

## Management

**Table 23. Management of Brachial Plexus Injuries***

| | Type | Treatment |
|---|---|---|
| **Closed Injuries** | Concussive/compressive | Usually improves (unless expanding mass, e.g. hematoma) |
| | Traction/stretch | If no continued insult, follow for 3-4 mo for improvement |
| | Obstetric palsy | Surgery if no significant improvement and/or residual paresis at 6 mo of age |
| **Open Injuries** | Sharp or vascular injury | Explore immediately in OR |

*All injuries listed require splinting as well as OT and PT consults to maintain ROM and function in the joint

# Craniofacial Injuries

- low velocity vs. high velocity injuries determine degree of damage
- fractures cause bruising, swelling, and tenderness → loss of function
- management: most can wait ~5 d for swelling to decrease before ORIF required

## Approach to Facial Injuries

- ATLS protocol
- inspect, palpate, clinical assessment for injury to underlying structures (e.g. facial nerve, bony injuries, septal hematoma, ocular involvement, etc.)
- tetanus prophylaxis
- radiological evaluation: CT scan with fine cuts through the orbit
- wound irrigation with NS/RL and remove foreign materials
- conservative debridement of detached or nonviable tissue
- repair at the time of presentation with 4-0 nylon sutures when the patient's general condition allows
- consider intracranial trauma; rule out skull fracture

Patients with major facial injuries are at risk of developing upper airway obstruction (displaced blood clots, teeth, or fracture fragments; swelling of pharynx and larynx; loss of support of hyomandibular complex → retroposition of tongue); also at risk of ocular injury

### Investigations

- CT (gold standard)
  - axial and coronal (specifically request 1.5 mm cuts): for fractures of upper and middle face, as well as mandible
  - indicated for significant head trauma, suspected facial fractures, and pre-operative assessment
- panorex radiograph: shows entire upper and lower jaw; best for isolated mandible fracture, but patient must be able to sit; however, if high clinical suspicion and negative panorex, CT should be done

**Signs of Basal Skull Fracture**
- Battle's sign (bruised mastoid process)
- Hemotympanum
- Raccoon eyes (periorbital bruising)
- CSF otorrhea/rhinorrhea

### Treatment Goals

- re-establish normal occlusion if occlusion is an issue
- normal eye function (extraocular eye movements and vision)
- restore stability of face and appearance
- consultation when indicated (dentistry, ophthalmology, neurosurgery)

## Mandibular Fractures

- two points of injury since it is a ring structure (includes fractures and dislocations)
- commonly at sites of weakness (condylar neck, angle of mandible)

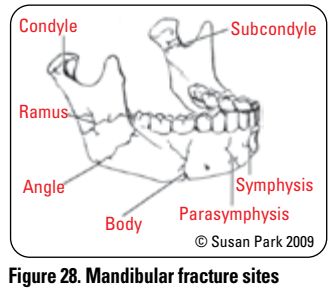


**Figure 28. Mandibular fracture sites**

### Etiology

- anterior force: bilateral fractures
- lateral force: ipsilateral subcondylar and contralateral angle or body fracture
- note: classified as open if fracture into tooth bearing area (alveolus)

### Clinical Features

- pain, swelling, difficulty opening mouth ("trismus")
- malocclusion, asymmetry of dental arch
- damaged, loose, or lost teeth
- palpable "step" along mandible
- numbness in V3 distribution
- intra-oral lacerations or hematoma (sublingual)
- chin deviating toward side of a fractured condyle

### Classification

**Table 24. Mandibular Fracture Classifications by Anatomic Region**

| | Areas/Boundaries |
|---|---|
| **Symphysis** | Midline of the mandible; between the central incisors from the alveolar process through the inferior border of the mandible |
| **Body** | From the symphysis to the distal alveolar border of the third molar |
| **Angle** | Triangular region between the anterior border of the masseter and the posterosuperior insertion of the masseter distal to the third molar |
| **Ramus** | Part of the mandible that extends posteriosuperiorly into the condylar and coronoid processes |
| **Condylar*** | Area of condylar process of mandible |
| **Subcondylar** | Area below the condylar neck (i.e. sigmoid notch) of the mandible |
| **Coronoid Process** | Area of the coronoid process of mandible |

*Most common mandibular fracture type

### Treatment
- maxillary and mandibular arch bars wired together (intramaxillary fixation) or ORIF ideally managed within 48 h as indicated by best current evidence
- antibiotics from initial presentation until at least 3 doses post-operatively; if late presentation, may consider treatment with antibiotics for an extended course

## Maxillary Fractures

**Table 25. Le Fort Classification**

| | Le Fort I | Le Fort II | Le Fort III |
|---|---|---|---|
| **Alternative Name** | Guérin fracture | Pyramidal fracture | Craniofacial dysjunction |
| **Type of Fracture** | Horizontal | Pyramidal | Transverse |
| **Structures Involved** | Piriform aperture | Nasal bones | Nasofrontal suture |
| | Maxillary sinus | Medial orbital wall | Zygomatofrontal suture |
| | Pterygoid plates | Maxilla | Zygomatic arch |
| | | Pterygoid plates | Pterygoid plates |
| **Anatomical Result** | Maxilla divided into 2 segments | Maxillary teeth and midsection of the maxilla separated from upper face | Entire midfacial skeleton detached from cranial base |

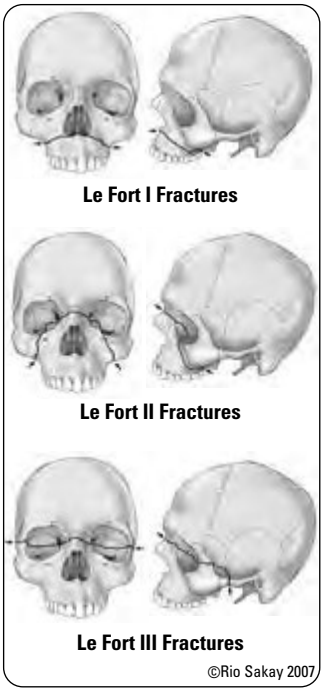


**Figure 29. Le Fort fractures**

## Nasal Fractures

### Etiology
- lateral force → more common, good prognosis
- anterior force → can produce more serious injuries
- most common facial fracture

### Clinical Features
- epistaxis/hemorrhage, deviation/flattening of nose, swelling, periorbital ecchymosis, tenderness over nasal dorsum, crepitus, septal hematoma, respiratory obstruction, subconjunctival hemorrhage

### Treatment
- treated for airway or cosmetic issues
- always inspect for and drain septal hematoma as this is a cause of septal necrosis and perforation – completed in the ER with small incision in the septal mucosa followed by packing
- closed reduction with Asch or Walsham forceps under anesthesia, pack nostrils with petroleum or nonadhesive gauze packing, nasal splint for 7 d
- best reduction immediately (<6 h) or when swelling subsides (5-7 d)
- rhinoplasty may be necessary later for residual deformity (30%)

## Zygomatic Fractures

### Classification
1. fracture restricted to zygomatic arch
2. depressed fracture of zygomatic complex (zygoma)
3. unstable fracture of zygomatic complex (tetrapod fracture) – separations occur at maxilla, frontal bone, temporal bone, and orbital rim

### Clinical Features
- 3 most common features (pathognomonic):
  - subconjunctival hemorrhage
  - periorbital ecchymosis (often associated with fractures of the orbital floor)
  - V2 numbness (infraorbital and superior dental nerves)
- flattening of malar prominence (view from above)
- pain over fractures on palpation
- palpable step deformity in bony orbital rim (especially inferiorly)
- ipsilateral epistaxis; trismus
- ophthalmologic evaluation if suspected globe injury

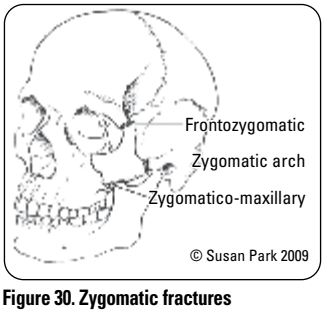


**Figure 30. Zygomatic fractures**

### Treatment
- if undisplaced, stable, and no symptoms, then soft diet; no treatment necessary
- undisplaced zygomatic arch fractures can be elevated using Gillies approach (leverage on the anterior part of the zygomatic arch via a temporal incision) or Keane approach (elevation through upper buccal sulcus incision) only if arch is not comminuted
- if arch is comminuted, ORIF is required
- stabilization often unnecessary
- ORIF for displaced or unstable fractures of zygomatic complex

# Orbital Floor Fractures

• see Ophthalmology, OP40

## Definition
• fracture of floor of orbit: may be a "pure blow-out fracture", which has an intact orbital rim, or can be associated with other fractures (orbital rim fracture and/or zygoma)

## Etiology
• blunt force to eyeball → sudden increase in intraorbital pressure (e.g. baseball or fist)

## Clinical Features
• defects in visual fields, decreased visual acuity, injury to globe
• periorbital edema and bruising, subconjunctival hemorrhage
• ptosis, exophthalmos, exorbitism, enophthalmos, or hypoglobus
• orbital rim step-offs with possible infraorbital nerve anesthesia
• vertical dystopia (abnormal displacement of the entire orbital cone in the vertical plane) – assessed by comparing the symmetry of the two pupils by a horizontal line running through the pupil of the unaffected eye
• orbital entrapment
  ▪ clinical diagnosis that is a surgical emergency
  ▪ diplopia with straight gaze: unable to look up past neutral (entrapment of inferior rectus), limited EOM
  ▪ severe pain or nausea and vomiting with upward globe movement
  ▪ requires urgent ophthalmology evaluation if there are associated visual acuity changes

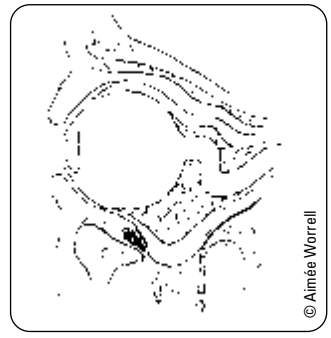


**Figure 31. Blow-out fracture**

## Investigations
• CT (diagnostic): axial and coronal views – with fine cuts through orbit; rounding of inferior rectus is a sign of orbital entrapment
• diagnostic maneuver for entrapment is forced duction test (pulling on inferior rectus muscle with forceps to ensure full ROM) under local anesthesia in the OR

## Treatment
• surgical repair indicated if: entrapment (urgent), any size defect with enophthalmos (if patient is bothered by it) or persistent diplopia (>10 d)
• reconstruction of orbital floor with bone graft or alloplastic material
• after repair, assess for diplopia (may require additional surgery for strabismus)

## Complications
• persistent diplopia
• enophthalmos

## Superior Orbital Fissure Syndrome
• fracture of SOF causing ptosis, proptosis, anesthesia in V1 distribution, and painful ophthalmoplegia (paralysis of CN III, IV, VI)
• uncommon complication seen in Le Fort II and III fractures (1/130)
• recovery time reported as 4.8-23 wk following operative reduction of fractures

## Orbital Apex Syndrome
• fracture through optic canal with involvement of CN II at apex of orbit
• symptoms are the same as SOF syndrome plus vision loss
• treatment is urgent decompression of fracture in optic canal (posterior craniotomy for decompression) or steroids

# Breast

## Anatomy

### Vascular Supply

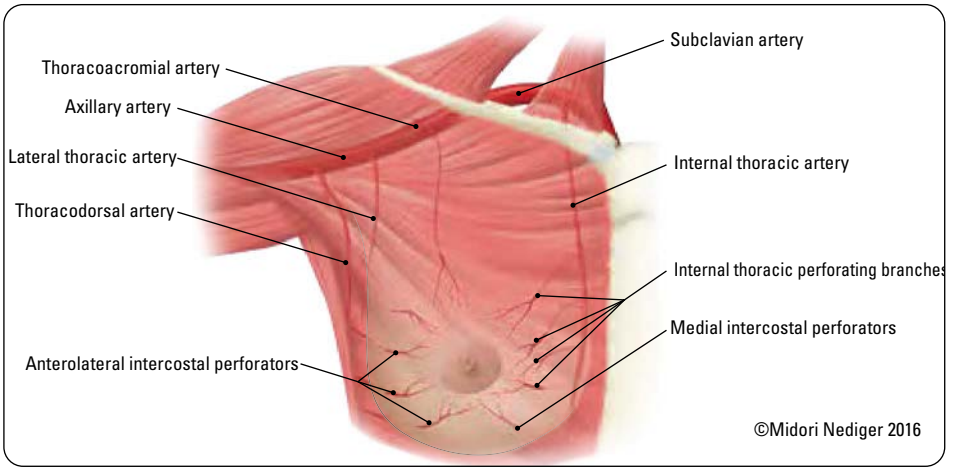



**Figure 32. Breast vasculature**

### Innervation

- innervated in a dermatomal pattern from branches of the thoracic intercostal nerves (T3-6)
  - medially innervated from anterior cutaneous branches of I-VI intercostal nerves
  - lateral innervated from lateral cutaneous nerve branches of II-VII intercostal nerves
- lateral and upper portions of the breast innervated by lower fibres of the cervical plexus (C3, C4)
- nipple areolar complex
  - supplied by anterior and lateral cutaneous branches of intercostal nerve IV
  - additional innervation by cutaneous branches of intercostal nerves III and VI

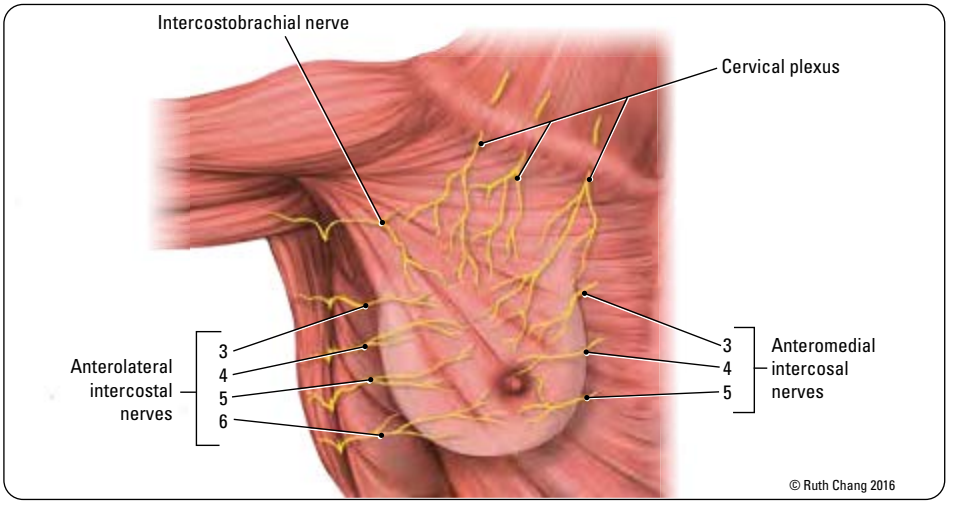



**Figure 33. Innervation of the breast**

# Breast Reduction

## Indications

- symptomatic (general symptoms)
  - musculoskeletal pain (back, strap, neck), chronic headache, paresthesia in upper limb, rashes under the breast, breast discomfort, and physical impairment
- breast reduction methods can be classified based on pedicle (i.e. blood supply to the nipple/areolar complex) and skin resection pattern (i.e. the resultant scar)

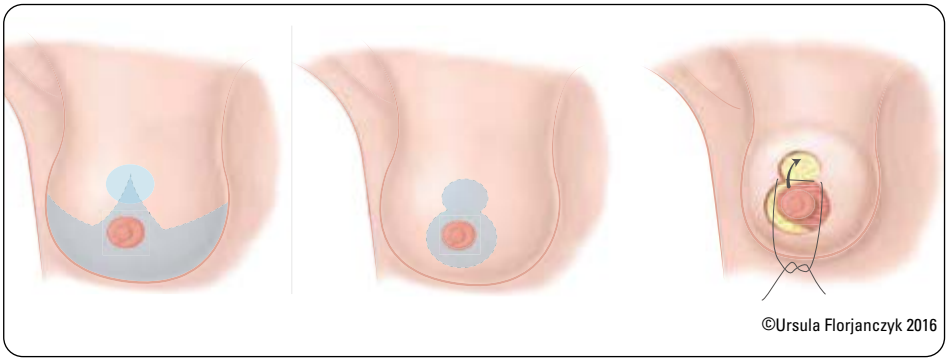



**Figure 34. Three diagrams of inverted T ("Wise") pattern reduction**

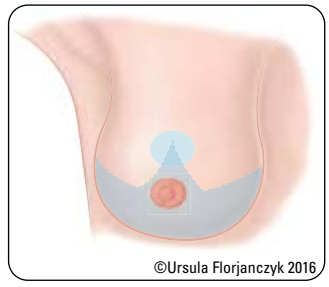



**Figure 35. Inverted T pattern**

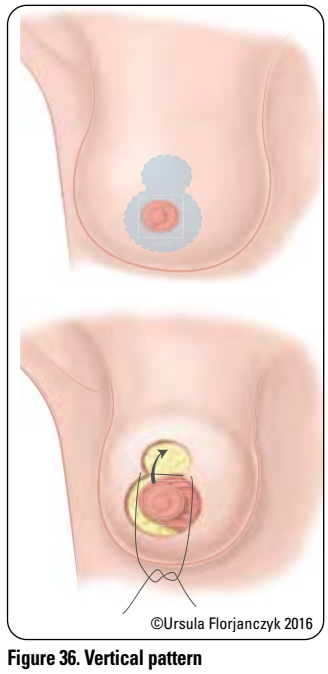



**Figure 36. Vertical pattern**

## Common Types of Pedicles

- inferior pedicle: derived from the fourth, fifth, and sixth intercostal perforators; most commonly used with the inverted T ("Wise") pattern reduction; versatile in small-large breast reduction
  - recommended pedicle width 6-8 cm, 8-10 cm in large breasts
- superior pedicle: derived from the internal mammary perforator of the second intercostal space
- medial pedicle: from horizontal bi-pedicle (Strombeck) techniques
  - blood supplied by internal mammary perforator and third intercostal and potentially fourth intercostal space
- superomedial pedicle: incorporate the descending artery from the second intercostal space as the medial pedicle base extends superolaterally to the breast meridian

**Table 26. Type of Skin Resections/Scar Options**

| | Indications | Description |
|---|---|---|
| **Inverted T Pattern** | Large breasts | Commonly used in association with inferior pedicle |
| | Breasts with poor quality skin that are challenging to remodel | Large portion of skin removed in horizontal and vertical direction |
| | | Skin integrity important to shape and hold breast parenchyma |
| **Vertical Pattern** | Skin must be healthy and easy to remodel | Used in association with superior or medial pedicle |
| | | Parenchyma needed to shape skin |
| | | No horizontal scar |
| | | Small to moderate reductions |

## Complications

- NAC necrosis
- sensory alteration of nipple (may vary with type of reduction pattern)
- unsatisfactory scarring, including hypertrophic or keloid scar
- wound healing complications (1-5% in healthy patients, higher in patients with elevated BMI)
- difficulty breastfeeding (controversial; potential issue in women of childbearing age)
- hematoma
- wound infection

# Mastopexy (Breast Lift)

### Definition
- aesthetic procedure of the breast used to correct for breast ptosis by modifying the contour and size of the breast along with elevating the position of the nipple

### Clinical Grading of Ptosis (Regnault Ptosis Grade Scale)
1. minor ptosis (Grade 1)
   - nipple at inframammary fold
2. moderate ptosis (Grade 2)
   - nipple below inframammary fold, but above lower breast contour
3. severe ptosis (Grade 3)
   - nipple below inframammary fold and at lower breast contour
4. glandular ptosis/pseudoptosis
   - ptosis of the lower pole of the breast where NAC is at or above the inframammary fold

### Choice of Incision
- mastopexy can be performed through the same incisions as breast reductions

# Breast Augmentation

### Definition
- procedure designed to increase the size of the breast

### Choice of Incision
- position of incision individualized since no single incision is best for all
- 3 commonly used types of incision: periareolar, inframammary crease, transaxillary

### Type of Implant
- silicone or saline-filled
- subclassified into various styles of surface and shape

### Location of Implant
- implants are commonly placed in the following positions:
  1. submuscular positions
     - implant placed below pectoralis major muscle
     - most commonly in patients that do not have enough tissue to cover the implant
  2. subglandular position
     - implant placed deep to glandular breast tissue but superficial to muscle
  3. subfascial
     - implant placed below the pectoralis fascia

### Complications
- breast implant-associated anaplastic large cell lymphoma (BiALCL)
  - increased risk of BiALCL with implants (only textured varieties)
  - presents as sudden onset of pain without injury, or as sudden onset of seroma on average of 7-8 yr after use of a textured implant for reconstruction or augmentation purposes
  - etiology: leading theory is that bacteria on implant form biofilm and tumour cells arise in response to the pathogen
  - 1/3000 risk
  - management: complete surgical removal of breast (mastectomy) and implant (including entire breast capsule); secondary management can include radiation therapy or brentuximab
- favourable clinical outcome if detected and treated early

# Gynecomastia

### Definition
- benign enlargement of the male breast due to proliferation of the glandular tissue

### Clinical Classification
- gynecomastia can be further classified into:
  1. idiopathic
  2. physiologic
     - neonatal: circulating maternal estrogens via placenta
     - pubertal: relative excess of plasma estradiol versus testosterone
     - elderly: decreased circulating testosterone, peripheral aromatization of testosterone to estrogen
  3. pathologic
     - endocrinopathies: excess estrogen, androgen deficiency, deficient production or action of testosterone
     - tumours
     - chronic disease: liver cirrhosis, renal
     - congenital/genetic: Klinefelter's syndrome, androgen resistance
  4. pharmacologic
     - drugs that may interefere with estrogen-testosterone balance including:
     - hormones (estrogens, gonadotropins, exogenous steroids)
     - antiandrogens
       - androgen receptor antagonists (steroidal and non-steroidal)
       - androgen synthesis inhibitors (5α-reductase inhibitors)
       - antigonadotropins (GnRH analogs, estrogens)
     - recreational drugs (marijuana, heroin, amphetamines)
     - antihypertensives (spironolactone)
  5. massive weight gain
     - for physical exam, investigations, and medical management (see Endocrinology, E47)

### Surgical Options
- surgery is the accepted management for gynecomastia
- surgery addresses the three components: breast, fat, skin
- often involves a combination of liposuction (to remove the fatty portion) and surgical excision through a small periareolar incision (to remove the glandular component)
- patients with significant skin excess may require skin excision as well

# Breast Reconstruction

- reconstruction of the breast after cancer or trauma to recreate the breast which is similar to the contralateral breast
- reconstruction can be performed immediately (at the same time as mastectomy), or delayed (as a separate surgery months or years after initial surgery)
- there are alloplastic and autogenous methods of reconstruction, each with its advantages and disadvantages

**Table 27. Timing of Immediate Reconstruction vs. Delayed Reconstruction**

| | Advantages | Disadvantages |
|---|---|---|
| **Immediate Reconstruction** | Generally best aesthetic outcome; may possibly preserve nipple if oncologically advisable<br>Does not require creation of additional skin<br>Tissues are not damaged from scarring | Skin viability assessment can be compromised<br>Longer surgical time<br>Less time for patient to consider surgical options |
| **Delayed Reconstruction** | More time for patients to discuss surgical options<br>Best for patients unable or unwilling to have immediate reconstruction<br>For patients who may be getting radiotherapy and undetermined post-surgery oncologic treatment<br>Provides option of contralateral surgery with reconstruction, if required (i.e. contralateral cancer) | Loss of skin, volume, lateral border of breast, and natural landmarks, including inframammary fold (makes surgery more challenging)<br>Resection of irradiated/scarred skin and associated wound healing complications, including risk of reconstructive failure<br>Likely requires more stages than immediate reconstruction for completion |

**Table 28. Alloplastic Reconstruction vs. Autogenous Reconstruction**

| | | Advantages | Disadvantages |
|---|---|---|---|
| **Alloplastic Reconstruction** | Single stage direct to implant (DTI) | Shorter surgery<br>May give a more complete or final result | Size restriction in reconstruction<br>Very few women meet criteria: grade 1 ptosis, small breast, skin-sparing mastectomy |
| | Two stage reconstruction with expander and implant | Less tension on mastectomy flaps compared to single-stage reconstruction with implants<br>Ability to increase skin to create breast and avoid use of flap<br>Some patient control over final outcome | Requires post-surgical procedures (requires patient to come to clinic for inflations)<br>Size of reconstruction limited to size and vascularity of mastectomy flaps |
| | Acellular dermal matrix and implant | Improved symmetry<br>Can cover areas of implant or tissue expander that cannot be covered by muscles | Greater risk of flap necrosis and infection |
| **Autogenous Reconstruction** | Latissimus Dorsi Flap | Reliable pedicle<br>Uses patient's own tissues<br>Provides skin and muscle<br>Possible to do muscle sparing procedure without flap compromise<br>Provides good amount of skin and muscle for reconstruction<br>Good option for delayed reconstruction, larger women, previously failed reconstruction, and to avoid complications of using abdominal wall | May also require implants for adequate volume |
| | TRAM (Transverse Rectus Abdominis Muscle) Flap | Can be done as a:<br>Fascial-sparing technique (Pedicled TRAM)<br>Free tissue transfer (Free TRAM)<br>Patient's own tissue (no implant)<br><br>Provides a good amount of tissue for transfer in most women<br>Provides a well-concealed scar | Second scar with second surgical site<br>Volume depends on patient's donor site<br><br>Pedicled TRAM:<br>Weakness in rectus abdominis with higher bulge rates<br><br>Free TRAM:<br>Similar complications to DIEPs<br>Less muscle used, decreased risk of hernia or bulge |
| | DIEP (Deep Inferior Epigastric Perforator) Flap | Method spares rectus abdominis muscle and fascia and should theoretically preserve innervation and continuity of abdominal wall | Requires microsurgical training for meticulous dissection of flap and appropriate choice of perforator<br>May not always be possible<br>Abdominal scarring and second wound |

# Nipple Areolar Complex Reconstruction

- nipple reconstruction is usually done as the final step when the patient is satisfied with breast mound creation
- reconstruction can be performed with local anesthetic since many women have decreased sensation in the mastectomy or breast flaps
- it can be done by either a flap, graft, or 3D tattoo

**Table 29. Types of Nipple Reconstruction**

| | Description | Advantages | Disadvantages |
|---|---|---|---|
| **Skate Flap** | Pedicle elevated above breast mound<br>Lateral aspects of flap are wrapped around central aspect of flap<br>Defect mainly closed by skin graft | Low complication rates | Donor site morbidity<br>May have loss of projection over time<br>Skin graft required |
| **Cv Flap** | Utilizes C flap and two V flaps for nipple reconstruction<br>Diameter of C flap becomes diameter of reconstructed nipple<br>Width of V flaps dictate projection of reconstructed nipple<br>CV closed with primary closure | No grafts required | Nipple size limited by flap dimensions<br>May have loss of projection over time<br>Tattooing required to match natural areola |
| **Nipple Graft** | Tissue commonly from contralateral nipple (nipple share) or labia<br>Two methods for nipple graft:<br>• Distal aspect of nipple removed transversely and defect closed with purse string suture<br>• Nipple divided in half longitudinally, folded over, and closed with primary closure | Nipple share is an excellent option in patients with contralateral nipple projection >1 cm | Donor site morbidity<br>Decreased contralateral nipple sensation<br><br>Labial graft: may be too dark |

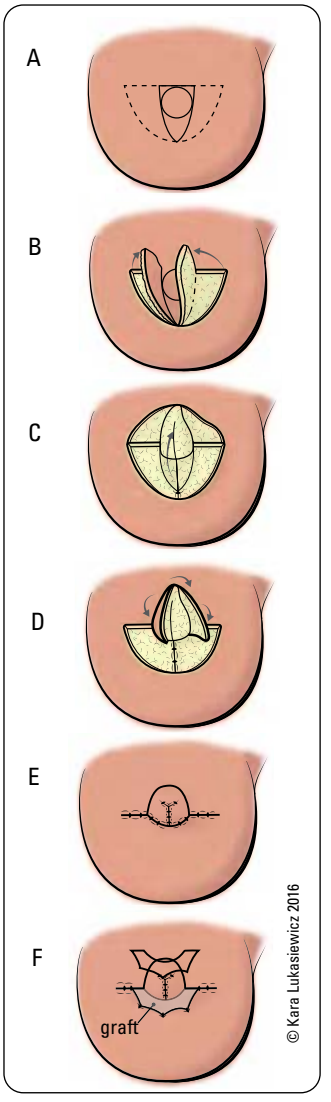



**Figure 37. Skate flap**
**E, skate flap with primary closure of donor site**
**F, with skin graft**

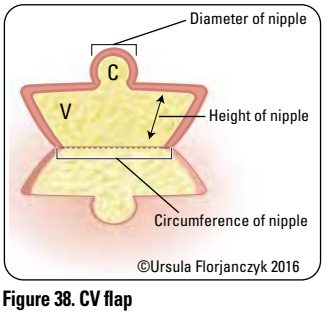



**Figure 38. CV flap**

**Table 30. Types of Areolar Reconstruction**

| | Description | Advantages | Disadvantages |
|---|---|---|---|
| **Tattoo** | Conducted 3-4 mo after nipple reconstruction when most of the projection has stabilized | Can provide more accurate colour matching with limited morbidity | May require touch-ups due to pigment fading over time with skin sloughing |
| **Skin graft** | Full thickness skin grafts, commonly from inner aspect of thigh or opposite areola | Provides texture and pigment resembling a natural areola | Donor site morbidity |

* Tattoo and skin grafting can be used in conjunction

# Aesthetic Surgery

## Aesthetic Procedures

**Table 31. Aesthetic Procedures**

| Location | Procedure | Description |
|---|---|---|
| **Head/Neck** | Hair transplants | Aesthetic improvement of hair growth patterns using hair follicle grafts or flaps |
| | Otoplasty | Surgical correction of protruding ears |
| | Forehead/Brow lift | Surgical procedure to lift the forehead and eyebrows |
| | Rhytidectomy | Surgical procedure to reduce wrinkling and sagging of the face and neck; "face lift" |
| | Blepharoplasty | Surgical procedure to shape or modify the appearance of eyelids by removing excess eyelid skin ± fat pads |
| | Rhinoplasty | Surgical reconstruction of the nose ± nasal airway |
| | Genioplasty | Chin augmentation via osteotomy or synthetic implant to improve contour |
| **Skin** | Chemical peel | Application of one or more exfoliating agents to the skin resulting in destruction of portions of the epidermis and/or dermis with subsequent tissue regeneration |
| | Dermabrasion | Skin resurfacing with a rapidly rotating abrasive tool; often used to reduce scars, irregular skin surfaces, and fine lines |
| | Laser resurfacing | Application of laser to the skin which ultimately results in collagen reconfiguration and subsequent skin shrinking and tightening; often used to reduce scars and wrinkles |
| | Injectable fillers | An injectable substance is used to decrease facial rhytids; can augment lips to create fuller appearance; substances include: collagen, fat, hyaluronic acid, and calcium hydroxyapatite (most common substances include hyaluronic acid and fat) |
| **Other** | Abdominoplasty | Removal of excess skin and repair of rectus muscle laxity (rectus diastasis); "tummy tuck" |
| | Calf augmentation | Augmentation of calf muscle with implants |
| | Liposuction | Surgical removal of adipose tissue for body contouring (not a weight loss procedure) |

# Pediatric Plastic Surgery

## Craniofacial Anomalies

**Table 32. Pediatric Craniofacial Anomalies**

| | Definition | Epidemiology | Clinical Features | Treatment |
|---|---|---|---|---|
| **Cleft Lip** | Failure of fusion of maxillary and medial nasal processes | 1 in 1000 live births (1 in 800 Caucasians, increased in Asians, decreased in Blacks)<br>M:F=2:1 | Classified as incomplete/complete and uni/bilateral; 2/3 cases: unilateral, left-sided, male | Surgery (3 mo): Millard Tennison-Randall, or Fisher (additional corrective surgeries usually required later on - especially for nasal deformity) |
| **Cleft Palate** | Failure of fusion of lateral palatine/median palatine processes and nasal septum | Isolated cleft palate: 0.5 per 1000 (no racial variation)<br>F>M | Classified as incomplete/complete and uni/bilateral<br>Isolated (common in females) or in conjunction with cleft lip (common in males) | Special bottles for feeding<br>Speech pathologist<br>Surgery (6-9 mo):<br>Von Langenbeck or Furlow Z-Plasty<br>ENT consult – often recurrent otitis media, requiring myringotomy tubes |
| **Craniosynostosis** | Premature fusion of ≥1 cranial sutures | 1 in 2000 live newborns;<br>M:F=52:48<br>Syndromes include: Crouzon's, Apert's, Saethre-Chotzen, Carpenter's, Pfeiffer's, Jackson-Weiss, and Boston-type syndromes | Primary (no known cause), or secondary (associated with a known cause or syndrome) | Multidisciplinary team (including neurosurgery, ENT, genetics, dentistry, pediatrics, SLP)<br>The type, timing, and procedure are dependent on which sutures (lambdoid, sagittal, etc.) are involved<br>Early surgery prevents secondary deformities<br>↑ ICP is an indication for emergent surgery |

# Congenital Hand Anomalies

**Table 33. American Society for Surgery of the Hand (ASSH) Classification of Congenital Hand Anomalies**

| Classification | Example | Features | Treatment |
|---|---|---|---|
| **Failure of Formation** | Transverse absence (congenital amputation) | At any level (often below elbow/wrist) | Early prosthesis |
| | Longitudinal absence (phocomelia) | Absent humerus<br>Thalidomide association | |
| | Radial deficiency (radial club hand) | Radial deviation<br>Thumb hypoplasia<br>M>F | Physiotherapy + splinting<br>Soft tissue release if splinting fails<br>Distraction osteogenesis (Ilizarov distraction)<br>± wedge osteotomy<br>Tendon transfer<br>Pollicization |
| | Thumb hypoplasia | Degree ranges from small thumb with all components to complete absence | Depends on degree – may involve no treatment, webspace deepening, tendon transfer, or pollicization of index finger |
| | Ulnar club hand | Rare, compared to radial club hand<br>Stable wrist | Splinting and soft tissue stretching therapies<br>Soft tissue release (if above fails)<br>Correction of angulation (Ilizarov distraction) |
| | Cleft hand | Autosomal dominant<br>Often functionally normal (depending on degree) | First web space syndactyly release<br>Osteotomy/tendon transfer of thumb (if hypoplastic) |
| **Failure of Differentiation/ Separation** | Syndactyly | Fusion of ≥2 digits<br>1/3000 live births<br>M:F=2:1<br>Classified as partial/complete<br>Simple (skin only) vs. complex (osseous or cartilaginous bridges) | Surgical separation before 6-12 mo of age<br>May require a skin graft to cover the fingers<br>Usually good result |
| | Symbrachydactyly | Short fingers with short nails at fingertips | Digital separation<br>Webspace deepening |
| | Camptodactyly | Congenital flexion contracture (usually at PIP, especially 5th digit) | Early splinting<br>Volar release<br>Arthroplasty (rarely) |
| | Clinodactyly | Radial or ulnar deviation<br>Often middle phalanx | None (usually); if severe, osteotomy with grafting |
| **Duplication** | Polydactyly | Congenital duplication of digits<br>May be radial (increased in Aboriginals and Asians) or central or ulnar (increased in Blacks) | Amputation of least functional digit<br>Usually >1 yr of age (when functional status can be assessed) |
| **Overgrowth** | Macrodactyly | Rare | None (if mild)<br>Soft tissue/bony reduction |
| **Undergrowth** | Brachydactyly | Short phalanges | Removal of nonfunctional stumps<br>Osteotomies/tendon transfers<br>Distraction osteogenesis<br>Phalangeal/free toe transfer |
| | Symbrachydactyly | Short webbed fingers | As above + syndactyly release |
| | Brachysyndactyly | | |
| **Constriction Band Syndrome** | i.e. amniotic (annular) band syndrome | Variety of presentations | Urgent release for acute, progressive edema distal to band in newborn<br>Other reconstruction is case specific |
| **Generalized Skeletal Abnormality** | Achondroplasia, Marfan's, Madelung's | Variety of presentations | Treatment depends on etiology |

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Notes

# PS Psychiatry

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# Acronyms

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 5-HT | serotonin | DA | dopamine | MET | motivational enhancement therapy | PTSD | post-traumatic stress disorder |
| ACh | acetylcholine | DBT | dialectical behavioural therapy | MSE | mental status examination | rTMS | repetitive transcranial magnetic stimulation |
| ACT | assertive community treatment | DZ | dizygotic | MST | magnetic stimulation therapy | SGA | second generation antipsychotics |
| ADHD | attention deficit hyperactivity disorder | ECT | electroconvulsive therapy | MZ | monozygotic | SNRI | serotonin and norepinephrine reuptake inhibitors |
| AN | anorexia nervosa | EPS | extrapyramidal symptoms | NA | Narcotics Anonymous | SS | serotonin syndrome |
| ASD | autism spectrum disorder | ERP | exposure with response prevention | NMS | neuroleptic malignant syndrome | SSRI | selective serotonin reuptake inhibitor |
| ASPD | antisocial personality disorder | EtOH | ethanol/alcohol | NOS | not otherwise specified | TCA | tricyclic antidepressant |
| BN | bulimia nervosa | GAD | generalized anxiety disorder | OCD | obsessive-compulsive disorder | TD | tardive dyskinesia |
| CBT | cognitive behavioural therapy | GMC | general medical condition | OCPD | obsessive-compulsive personality disorder | | |
| CD | conduct disorder | IPT | interpersonal therapy | | | | |
| CRA | community reinforcement approach | MAOi | monoamine oxidase inhibitor | ODD | oppositional defiant disorder | | |
| CT | cognitive therapy | MDD | major depressive disorder | PD | personality disorder | | |
| CTO | community treatment order | MDE | major depressive episode | PDD | pervasive developmental disorder | | |

# Psychiatric Assessment

## History

### Identifying Data
- necessary: name, age, sex/gender, marital status, occupation/source of financial support, place/type of residency
- adjunct: makeup of household, education, ethnicity, nationality, immigration history (if applicable), religion, current professional supports (GP, psychiatrist, case manager, therapist, etc), referral source, known or unknown to treatment team

### Reliability of Patient as a Historian
- indicate if, and for what content; utilize collateral source (i.e. parent, teacher, partner) if patient unable/unwilling to be interviewed

### Chief Complaint
- in patient's own words, with duration of symptoms

### History of Present Illness
- reason for seeking help (that day) and hopes/expectations for treatment
- current symptoms (onset, duration, fluctuation, progression, and course) and relevant associated symptoms (pertinent positives and negatives)
- potential precipitants for current problem, stressors, supports
- functional status: consider impact of current problems on personal care and survival, family functioning, occupational functioning, and broad social functioning
- safety screen: endangering self or others, dependents at home (i.e. children, pets), ability to drive safely, ability to care for self (i.e. eating, hygiene, taking medications)
- active medical problems

### Psychiatric Functional Inquiry
- mood: depression, mania
- anxiety: worries, panic attacks, phobias, or social anxiety
- history of trauma
- obsessive-compulsive: obsessions, compulsions
- psychosis: hallucinations, delusions
- risk assessment: suicidal ideation, plan, intent, and history of attempts (see Suicide, PS5)
- organic: illness, dementia

### Past Psychiatric History
- all previous psychiatric diagnoses, psychiatric contacts, treatments (pharmacological and non-pharmacological), and hospitalizations
- include past suicide attempts, severity, necessity for medical intervention

### Substance Use History
- smoking, EtOH/drug use or withdrawal
- past treatments, periods of sobriety

### Past Medical/Surgical History
- all medical, surgical, neurological (i.e. head trauma, seizures), and psychosomatic illnesses
- current medications, doses, adherence, allergies

### Family Psychiatric/Medical History
- any past or current psychiatric illnesses and hospitalizations, suicide attempts, and substance abuse
- if relevant: any past medical or genetic illness

**Screening Questions for Major Psychiatric Disorders**
- Have you been feeling down, depressed or hopeless?
- Do you feel anxious or worry about things?
- Has there been a time in your life where you have felt euphoric, extremely talkative, had a lot of energy, and a decreased need for sleep?
- Do you see or hear things that you think other people cannot?
- Have you ever thought of harming yourself or killing yourself?

**Psychiatric Functional Inquiry**

**MOAPS**
**M**ood
**O**rganic (e.g. substances and organic disease)
**A**nxiety
**P**sychosis
**S**afety

**Always Remember to Ask About Abuse**
See Family Medicine, FM26

### Past Personal/Developmental History (as relevant)

- family members: ages, occupations, personalities
- relationships with parents/siblings/partner/friends
- prenatal and perinatal history (desired vs. unwanted pregnancy, maternal and fetal health, domestic violence, maternal substance use and exposures, complications of pregnancy/delivery)
- early childhood to age 3 (developmental milestones, activity/attention level, family stability, or attachment figures)
- middle childhood to age 11 (school performance, peer relationships, behavioural challenges)
- late childhood to adolescence (drugs/alcohol, legal problems, peer and family relationships)
- history of physical or sexual abuse
- adulthood (education, employment, relationships)
- personality before current illness, or recent changes in personality
- psychosexual history (puberty, first sexual encounter, romantic relationships, gender roles, and sexual dysfunction)
- problems/encounters with the legal system

## Mental Status Exam

### General Appearance

- posture, gait, grooming, hygiene, manner of dress, body habitus, facial expression, chronological vs. apparent age, and relaxed or in distress, alertness

### Attitude

- disposition in interview (i.e. uncooperative, suspicious, or hostile)

### Behaviour

- psychomotor activity (agitation, retardation), abnormal movements or lack thereof (tremors, akathisia, tardive dyskinesia, paralysis), attention level and eye contact

### Speech

- rate (i.e. pressured, slowed), rhythm/fluency, volume, tone, articulation, quantity, spontaneity

### Mood and Affect

- mood: subjective emotional state (in patient's own words)
- affect: objective emotional state inferred from emotional responses to stimuli; described in terms of
  - quality (euthymic, depressed, elevated, anxious, irritable)
  - range (full, restricted, flat, blunted)
  - stability (fixed, labile)
  - mood congruence (inferred by comparing the patient's subjective mood with their affect)
  - appropriateness to thought content
- many clinicians use a 0-10 scale (0; worst; 10: best) when rating mood to get a subjective norm for each patient that can help to monitor changes over time and with treatment

### Thought Process/Form

- coherence (coherent, incoherent)
- logic (logical, illogical)
- stream
  - goal-directed: clearly answers questions in a linear, organized, logical fashion
  - circumstantial: speech that is indirect and delayed in reaching its goal; eventually comes back to the point
  - tangential: speech is oblique or irrelevant; does not come back to the original point
  - loosening of associations/derailment: illogical shifting between topics
  - flight of ideas: quickly skipping from one idea to another where the ideas are marginally connected, usually associated with mania
  - word salad: jumble of words lacking meaning or logical coherence
- perseveration: repetition of the same verbal or motor response to stimuli
- echolalia: repetition of phrases or words spoken by someone else
- thought blocking: sudden cessation of flow of thought and speech
- clang associations: speech based on sound such as rhyming or punning
- neologism: use of novel words or of existing words in a novel fashion

### Thought Content

- suicidal ideation/homicidal ideation
  - frequency and pervasiveness of thoughts, formulation of plan, means to plan, intent, active vs. passive, protective factors
- preoccupations, ruminations: reflections/thoughts at length, not fixed or false
- obsession: recurrent and persistent thought, impulse, or image which is intrusive or inappropriate and unwanted
  - cannot be stopped by logic or reason
  - causes marked anxiety and distress
  - common themes: contamination, orderliness, sexual, pathological doubt/worry/guilt



**Mental Status Exam**

**ASEPTIC**
**A**ppearance and behaviour
**S**peech
**E**motion (mood and affect)
**P**erception
**T**hought content and process
**I**nsight and judgment
**C**ognition



The MSE is analogous to the physical exam. It focuses on current signs, affect, behaviour, and cognition



**Spectrum of Affect**
Full > Restricted > Blunted > Flat



There is poor correlation between clinical impression of suicide risk and frequency of attempts



**Cognitive Assessment**
**Use MMSE to assess**
- Orientation (time and place)
- Memory (immediate and delayed recall)
- Attention and concentration
- Language (comprehension, reading, writing, repetition, naming)
- Spatial ability (intersecting pentagons)

Gross screen for cognitive dysfunction: Total score is out of 30; <26 abnormal, 20-26 mild, 10-19 moderate, <10 severe



The key to differentiating obsessions and delusions is that obsessions are usually ego dystonic, meaning unwanted and not fitting in with a person's goals and self-image, while delusions are ego syntonic



**Delusions**
- Persecutory: belief that others are trying to cause harm to you
- Reference: interpreting publicly known events/celebrities as having direct reference to you
- Erotomania: belief that another is in love with you
- Grandiose: belief that he or she has special powers, talents or abilities
- Religious: belief of receiving instructions/powers from a higher being; of being a higher being
- Somatic: belief that you have a physical disorder/defect
- Nihilistic: belief that things do not exist; a sense that everything is unreal

- magical thinking (i.e. superstition, belief that thinking something will make it happen), normal in children and certain cultures
- ideas of reference: similar to delusion of reference, but less fixed (the reality of the belief is questioned)
- overvalued ideas: unusual/odd beliefs that are not of delusional proportions
- first rank symptoms of schizophrenia: thought insertion/withdrawal/broadcasting
- delusion: a fixed false belief that is out of keeping with a person's cultural or religious background and is firmly held despite incontrovertible proof to the contrary

### Perception
- hallucination: sensory perception in the absence of external stimuli that is similar in quality to a true perception
  - auditory (most common), visual, gustatory, olfactory, tactile
- illusion: misperception of a real external stimulus (such as mistaking a coat on a rack as a person late at night)
- depersonalization: change in self-awareness such that the person feels unreal, distant, or detached from his or her body, and/or unable to feel emotion
- derealization: feeling that the world/outer environment is unreal

### Cognition
- level of consciousness (alert, reduced, obtunded)
- orientation: time, place, person
- memory: immediate, recent, or remote
- global evaluation of intellect (below average, average, above average, in keeping with person's education)
- intellectual functions: attention, concentration, calculation, abstraction (proverb interpretation, similarities test), language, communication
- MMSE/MOCA useful as standard screening assessments of cognition

### Insight
- patient's ability to realize that he or she has a physical or mental illness and to understand its implications (none, limited, partial, or full)

### Judgment
- patient's ability to understand relationships between facts and draw conclusions that determine one's actions

**Assessing Insight and Judgment**

**Insight**
- Do you think that you have a mental illness?
- Why are you taking this medication? What would happen if you stopped taking it?
- Why are you in the hospital?

**Judgment**

Can be observed from collected history and patient's appearance and actions
- Is he/she dressed appropriately for the weather?
- Is he/she acting appropriately in the given situation?
- Is he/she taking care of self and/or dependents?

# Assessment and Plan

### Historical Multiaxial Model
- since DSM-5, this model is no longer used for psychiatric diagnosis. Instead, relevant psychiatric and medical diagnoses are simply listed. Nevertheless, we offer it here as a possible framework for psychiatric patient assessment, as many physicians still employ it

### Multiaxial Assessment
- Axis I: DSM-5 diagnoses (preferred and differential)
- Axis II: personality disorders, intellectual disability
- Axis III: medical conditions potentially relevant to understanding/management of the mental disorder
- Axis IV: psychosocial and environmental issues
- Axis V: Global Assessment of Functioning (GAF, 0 to 100) incorporating effects of axes I to IV

### After History and MSE, the assessment and plan is recorded

### Assessment/Problem Formulation
- identify predominant symptom cluster (mood, anxiety, psychosis, organic) causing the most distress/interference, persist when other symptom categories not present (i.e. psychosis in the absence of mood symptoms)
- dominating symptoms will direct differential
- consider current issues as they relate to an individual considering three domains: biological, psychological, and social
- for each category: predisposing, precipitating, perpetuating, and protecting factors are considered

Always rule out substance use and organic causes before considering psychiatric causes

### Approach to Management
- consider short-term and long-term, and three types: biological (i.e. pharmacotherapy, ECT), psychological (i.e. CBT), and social (i.e. supports, finance/employment/return to work, social activity, medication coverage, psychotherapy coverage)

# Suicide

## Importance
- must be screened for in every encounter; part of risk assessment along with violent/homicidal ideation

## Approach
- ask every patient: i.e. "Have you had any thoughts of wanting to harm or kill yourself?"
- classify ideation
  - passive ideation ("death wish"): would rather not be alive but has no active plan for suicide
    - i.e. "I'd rather not wake up" or "I would not mind if a car hit me"
  - active ideation
    - i.e. "I think about killing myself"
- assess risk
  - plan: "Do you have a plan as to how you would end your life?"
  - intent: "Do you think you would actually carry out this plan?" "If not, why not?"
  - past attempts: number, lethality, outcome, medical intervention, while intoxicated?, precipitants
- assess suicidal ideation
  - onset and frequency of thoughts: "When did this start?" or "How often do you have these thoughts?"
  - control over suicidal ideation: "How do you cope when you have these thoughts?" "Could you call someone for help?"
  - intention: "Do you want to end your life?" or "Do you wish to kill yourself?"
  - intended lethality: "What do you think would happen if you actually took those pills?"
  - access to means: "How will you get a gun?" or "Which bridge do you think you would go to?"
  - time and place: "Have you picked a date and place? Is it in an isolated location?"
  - provocative factors: "What makes you feel worse (i.e. being alone)?"
  - protective factors: "What keeps you alive (i.e. friends, family, pets, faith, therapist)?"
  - final arrangements: "Have you written a suicide note? Made a will? Given away your belongings?"
  - practiced suicide or aborted attempts: "Have you ever put the gun to your head?" "Held the medications in your hand?" "Stood at the bridge?"
  - ambivalence: "I wonder if there is a part of you that wants to live, given that you came here for help?"
  - determine level of risk and develop treatment/safety plan

**Suicidal Ideation Assessment**
- Asking patients about suicide will not give them the idea or the incentive to die by suicide
- The best predictor of completed suicide is a history of attempted suicide
- The most common psychiatric disorders associated with completed suicide are mood disorders and alcohol abuse

## Assessment of Suicide Attempt
- setting (isolated vs. others present/chance of discovery)
- planned vs. impulsive attempt, triggers/stressors
- substance use/intoxication
- medical attention (brought in by another person vs. brought in by self to ED)
- time lag from suicide attempt to ED arrival
- expectation of lethality, dying
- reaction to survival (guilt/remorse vs. disappointment/self-blame)
- evidence of escalation in potential lethal means

## Epidemiology
- attempted:completed = 20:1 (100:1 in younger persons; 4:1 in older persons)
- M:F = 1:4 for attempts, 3:1 for completed

## Risk Factors
- epidemiologic factors
  - age: increases after age 14, second most common cause of death for ages 15-24, highest rates of completion in persons >75 yr
  - sex: male
  - race/ethnic background: white or Indigenous Canadians
  - marital status: widowed/divorced
  - living situation: alone; no children <18 yr old in the household
  - other: stressful life events, or access to firearms
- psychiatric factors
  - past suicide attempt(s)
  - eating disorders
  - bipolar disorder
  - major depression
  - mixed drug abuse
  - panic disorder
  - schizophrenia
  - personality disorder
  - alcohol abuse
- psychosocial factors
  - recent, severe stressful life event

**Suicide Risk Factors**

**SAD PERSONS**
**S**ex (male)
**A**ge >60 yr old
**D**epression
**P**revious attempts
**E**thanol abuse
**R**ational thinking loss (delusions, hallucinations, hopelessness)
**S**uicide in family
**O**rganized plan
**N**o spouse (no support systems)
**S**erious illness, intractable pain

- psychiatric disorders
  - mood disorders (15% lifetime risk in depression; higher in bipolar)
  - anxiety disorders (especially panic disorder)
  - schizophrenia (10-15% risk)
  - substance abuse (especially alcohol – 15% lifetime risk)
  - eating disorders (5% lifetime risk)
  - adjustment disorder
  - conduct disorder
  - personality disorders (borderline, antisocial)
- past history
  - prior suicide attempt
  - family history of suicide attempt/completion

## Clinical Feature

- symptoms associated with suicide:
  - hopelessness
  - anhedonia
  - insomnia
  - severe anxiety
  - impaired concentration
  - psychomotor agitation

## Management

- proper documentation of the clinical encounter and rationale for management is essential
- higher risk (patients with a plan and intention to act, have access to lethal means, recent social stressors, and symptoms suggestive of a psychiatric disorder)
  - hospitalization to be strongly considered
  - do not leave patient alone; remove potentially dangerous objects from room
  - if patient refuses to be hospitalized, complete form for involuntary admission (Form 1) and must give patient Form 30 to notify them of their admission
- lower risk (patients who are not actively suicidal, with no active plan or access to lethal means)
  - discuss protective factors and supports in their life, remind them of what they live for, promote survival skills that helped them through previous suicide attempts
  - make a safety plan that could include an agreement that they will:
    - not harm themselves
    - avoid alcohol, drugs, and situations that may trigger suicidal thoughts
    - follow-up with you at a designated time
    - contact a health care worker, call a crisis line, or go to an emergency department if they feel unsafe or if their suicidal feelings return or intensify
- patients with depression: consider hospitalization if symptoms severe or if psychotic features are present; otherwise outpatient treatment with good supports and SSRIs/SNRIs
- patients with alcohol- or substance-related issues: suicidality usually resolves with abstinence for a few days; if not, suspect depression
- patients with personality disorders: crisis intervention, may or may not hospitalize
- patients with schizophrenia/psychosis: hospitalization might be necessary
- patients with parasuicidal behaviours/self-mutilation: long-term psychotherapy with brief crisis intervention when necessary

# Psychotic Disorders

## Definition

- characterized by a significant impairment in reality testing
- positive symptoms
  - delusions or hallucinations (with or without insight into their pathological nature)
  - disorganized behaviours
  - formal thought disorder
- negative symptoms
  - affective flattening
  - anhedonia
  - avolition
  - alogia
  - asociality

# Differential Diagnosis of Psychosis

## Approach

- differentiate among psychotic disorders and distinguish them from other primary diagnoses with psychotic features
- consider symptoms, persistence, and time
- symptoms: the primary diagnosis needs full criteria to be met
  - mood: depressive episodes with psychotic features, manic episodes with psychotic features
  - psychotic: consider symptoms in Criterion A of schizophrenia (see *Criteria for Schizophrenia*)
- persistence: is there a time when certain symptom clusters are present without other clusters?
  - i.e. if there is a period of time with mood symptoms but not psychotic symptoms, consider mood disorder
  - i.e. if two weeks during which psychotic symptoms persist in the absence of mood symptoms, consider schizoaffective disorder
  - i.e. if long periods with psychotic symptoms and brief or rare mood symptoms, consider schizophrenia
- time: how long have the symptoms been present?

**Table 1. Differentiating Psychotic Disorders**

| Disorder | Psychotic Symptoms | Duration |
|---|---|---|
| **Brief Psychotic Disorder** | ≥1 positive symptoms of criterion A | <1 mo |
| **Schizophreniform Disorder** | Criterion A | 1-6 mo |
| **Schizophrenia** | Criterion A | >6 mo |
| **Schizoaffective Disorder** | Criterion A + major mood episode, but ≥2 wk psychotic without mood symptoms | >1 mo |
| **Delusional Disorder** | Non-bizarre delusions (±hallucinations) | >1 mo |
| **Substance-Induced Psychotic Disorder** | Delusions or hallucinations | During intoxication/withdrawal, resolve in less than 1 mo without use |
| **2º to Mood Disorder** | Mood symptoms dominant + delusions/ hallucinations (mood congruent) | Psychosis may be present for the duration of the mood episode |

## Relevant Investigations

- CBC, electrolytes (including extended lytes), creatinine, glucose, urinalysis, urine drug screen, TSH, Vit B12
- LFTs, fasting lipids, HbA1C to obtain baseline levels prior to antipsychotic initiation
- ECG (several antipsychotics affect cardiac conduction)
- If clinically indicated, order infectious work-up, inflammatory markers, brain imaging

**Delusions:** fixed, false beliefs
**Hallucinations:** perceptual experiences without an external stimulus

**Duration of Time Differentiates the following 3 Psychotic Disorders**

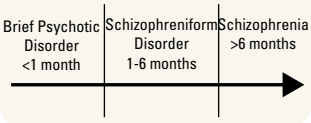



**Figure 1. Differentiating psychotic disorders by duration**

**Ddx for Psychosis**

- Primary psychotic disorders: schizophrenia, schizophreniform, brief psychotic, schizoaffective, delusional disorder
- Mood disorders: major depressive disorder with psychotic features, bipolar disorder (manic or depressive episode with psychotic features)
- Personality disorders: schizotypal, schizoid, borderline, paranoid, obsessive-compulsive (they predispose to psychosis but presence of psychotic symptoms require another diagnosis)
- General medical conditions: tumour, head trauma, dementia, delirium, metabolic, infection, stroke, temporal lobe epilepsy
- Substance-induced psychosis: intoxication or withdrawal, prescribed medications, toxins

**Management of Acute Psychosis and Mania**

- Ensure safety of self, patient, and other patients
- Have an exit strategy
- Decrease stimulation
- Assume a non-threatening stance
- IM medications (benzodiazepine + antipsychotic) often needed as patient may refuse oral medication
- Physical restraints may be necessary
- Do not use antidepressants or stimulants

**Relationship Between Duration of Untreated Psychosis (DUP) and Outcome in First-Episode Schizophrenia**
*Am J Psychiatry* 2005;162:1785-1804
**Purpose**: To review the association between DUP and symptom severity at first treatment contact, and between DUP and treatment outcomes.
**Methods**: Critical review and meta-analysis of studies involving patients with non-affective psychotic disorders at or close to first treatment.
**Results**: 43 studies with 4177 patients were included. Shorter DUP was associated with greater response to antipsychotic treatment, as measured by global psychopathology, positive symptoms, negative symptoms, and functional outcomes. At the time of treatment initiation, longer DUP was associated with the severity of negative symptoms but not with the severity of positive symptoms, global psychopathology, or neurocognitive function.
**Conclusions**: DUP may be a potentially modifiable prognostic factor.

# Schizophrenia

## DSM-5 DIAGNOSTIC CRITERIA FOR SCHIZOPHRENIA

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

A. two (or more) of the following, each present for a significant portion of time during a 1 mo period (or less if successfully treated). At least one of these must be (1), (2), or (3)
   1. delusions
   2. hallucinations
   3. disorganized speech (i.e. frequent derailment or incoherence)
   4. grossly disorganized or catatonic behaviour
   5. negative symptoms (i.e. diminished emotional expression or avolition)

B. decreased level of function: for a significant portion of time since onset, one or more major areas affected (i.e. work, interpersonal relations, self-care) is markedly decreased (or if childhood/adolescent onset, failure to achieve expected level)

C. at least 6 mo of continuous signs of the disturbance. Must include at least 1 mo of symptoms (or less if successfully treated) that meet Criterion A (i.e. active-phase symptoms) and may include periods of prodromal or residual symptoms, during which, disturbance may manifest by only negative symptoms or by two or more Criterion A symptoms present in an attenuated form (i.e. odd beliefs, unusual perceptual experiences)

D. rule out schizoaffective disorder and depressive or bipolar disorder with psychotic features because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness

E. rule out other causes: GMC, substances (i.e. drug of abuse, medication)

F. if history of autism spectrum disorder or communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least 1 mo (or less if successfully treated)

- **specifiers**: type of episode (i.e. first episode, multiple episodes, continuous), with catatonia, current severity based on quantitative assessment of primary symptoms of psychosis (in acute episode, in partial remission, in full remission)

### Epidemiology

- prevalence: 0.3-0.7%, M:F = 1:1
- mean age of onset: females late-20s to 40s; males early- to mid-20s (some cases with late onset)
- suicide risk: 10% die by suicide, 30% attempt suicide

### Etiology

- multifactorial: disorder is a result of interaction between both biological and environmental factors
  - genetic: 40% concordance in monozygotic (MZ) twins; 46% if both parents have schizophrenia; 10% of dizygotic (DZ) twins, siblings, children affected; vulnerable genes include Disrupted-in-Schizophrenia 1 (DISC1); neuregulin 1 (NRG 1); dystrobrevin binding protein / dysbindin (DTNBP1); catechol-O-methyltransferase (COMT); d-amino acid oxidase activator (DAOA); metabotropic glutamate receptor 3 (GRM3); and brain-derived neurotrophic factor (BDNF)
  - neurochemistry ("dopamine hypothesis"): excess activity in the mesolimbic dopamine pathway may mediate the positive symptoms of psychosis, while decreased dopamine in the prefrontal cortex may mediate negative and cognitive symptoms. GABA, glutamate, and ACh dysfunction are also thought to be involved
  - neuroanatomy: decreased frontal lobe function; asymmetric temporal/limbic function; decreased basal ganglia function; subtle changes in thalamus, cortex, corpus callosum, and ventricles; cytoarchitectural abnormalities
  - neuroendocrinology: abnormal growth hormone, prolactin, cortisol, and ACTH
  - neuropsychology: global defects seen in attention, language, and memory suggest disrupted connectivity of neural networks
  - environmental: indirect evidence of cannabis use, geographical variance, winter season of birth, obstetrical complications, and prenatal viral exposure

### Pathophysiology

- neurodegenerative theory: natural history may be a rapid or gradual decline in function and ability to communicate
  - glutamate system may mediate progressive degeneration by excitotoxic mechanism which leads to production of free radicals
- neurodevelopmental theory: abnormal development of the brain from prenatal life
  - neurons fail to migrate correctly, make inappropriate connections, and apoptosis in later life

### Comorbidity

- substance-related disorders
- anxiety disorders
- reduced life expectancy secondary to medical comorbidities (i.e. obesity, diabetes, metabolic syndrome, CV/pulmonary disease)

**Disorganized Behaviours in Schizophrenia**

- Catatonic stupor: fully conscious, but mute, and unresponsive, immobile, , maintaining bizarre positions for a long time
- Catatonic excitement: uncontrolled and aimless motor activity, extreme agitation
- Stereotypy: repeated but non-goal-directed movement (i.e. rocking)
- Mannerisms: goal-directed activities that are odd or out of context (i.e. grimacing)
- Echopraxia: imitates movements and gestures of others
- Automatic obedience: carries out simple commands in robot-like fashion
- Negativism: refuses to cooperate with simple requests for no apparent reason
- Inappropriate affect, neglect of self-care, other odd behaviours (random shouting)

**Cannabis Use and Earlier Onset of Psychosis**

Arch Gen Psychiatry 2011;68:555-561

**Purpose**: To examine the extent to which cannabis, alcohol and other psychoactive drugs affect the age of onset of psychosis.

**Method**: A systematic review and meta-analysis. English studies were included that compared two cohorts: patients who used substances versus patients who do not use substance.

**Results**: 83 studies were included. Age of onset in cannabis users was 2.7 years younger than in nonusers. For broadly defined substance use, age of onset of psychosis was 2.0 years earlier than for nonusers. Alcohol use was not associated with significantly earlier age of psychosis.

**Conclusions**: These results provide evidence that cannabis plays a role in earlier onset of psychosis.

### Management of Schizophrenia

- biological / somatic
  - acute treatment and maintenance: antipsychotics (risperidone, aripiprazole, haloperidol, paliperidone; clozapine if resistant); regimens of IM q2-4 wk used in severe cases to improve adherence
  - adjunctive: ± mood stabilizers (for aggression/impulsiveness - lithium, valproate, carbamazepine) ± anxiolytics ± ECT
  - treat for at least 1-2 years after the first episode, at least 5 years after multiple episodes (relapse causes severe deterioration)
- psychosocial
  - psychotherapy (individual, family, group), supportive, CBT (see Table 14, PS41)
  - ACT (Assertive Community Treatment): mobile mental health teams that provide individualized treatment in the community and help patients with medication adherence, basic living skills, social support, job placements, resources
  - social skills training, employment programs, disability benefits
  - housing (group home, boarding home, transitional home)

### Course and Prognosis

- majority of individuals display some type of prodromal phase
- course is variable: some individuals have exacerbations and remissions while others remain chronically ill; accurate prediction of the long-term outcome is not possible
- positive symptoms typically diminish with treatment; negative symptoms may be prominent early in the illness or may become more prominent and more disabling later on
- over time: 1/3 improve, 1/3 remain the same, 1/3 worsen

**Good Prognostic Factors**

- Acute onset
- Shorter duration of prodrome
- Female gender
- Good cognitive functioning
- Good premorbid functioning
- No family history
- Presence of affective symptoms
- Absence of structural brain abnormalities
- Good response to drugs
- Good support system

## Schizophreniform Disorder

### Diagnosis

Adopted/summarized from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

- criteria A, D, and E of schizophrenia are met; an episode of the disorder lasts for at least 1 mo but less than 6 mo
- if the symptoms have extended past 6 mo the diagnosis becomes schizophrenia
- specifiers: with/without good prognostic features (i.e. acute onset, confusion, good premorbid functioning, absence of blunt/flat affect), with catatonia, current severity based on quantitative assessment of primary symptoms of psychosis

### Treatment

- similar to acute schizophrenia

### Prognosis

- better than schizophrenia; begins and ends more abruptly; good pre- and post-morbid function

## Brief Psychotic Disorder

### Diagnosis

Adopted/summarized from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

- criteria A1-A4, D, and E of schizophrenia are met; an episode of the disorder lasts for at least 1 d, but less than 1 mo with eventual full return to premorbid level of functioning
- specifiers: with/without marked stressors, with postpartum onset, with catatonia, current severity
- can occur after a stressful event or postpartum (see *Postpartum Mood Disorders*, PS14)

### Treatment

- secure environment, antipsychotics, and anxiolytics

### Prognosis

- good, self-limiting, should return to pre-morbid function within 1 mo

## Schizoaffective Disorder

### DSM-5 DIAGNOSTIC CRITERIA FOR SCHIZOAFFECTIVE DISORDER

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A. concurrent psychosis (criterion A of schizophrenia) and major mood episode - uninterrupted period of illness
B. delusions or hallucinations for 2 or more wk in the absence of a major mood episode during the lifetime duration of the illness
C. major mood episode symptoms are present for the majority of the total duration of the active and residual periods of the illness
D. the disturbance is not attributable to the effects of a substance or another medical condition

- **specifiers**: bipolar type, depressive type, with catatonia, type of episode, severity

Non-bizarre delusions involve situations that could occur in real life (i.e. being followed, poisoned, loved at a distance) Bizarre delusions involve situations that cannot occur in real life (i.e. being kidnapped by aliens, having one's organs stolen)

### Epidemiology
- one-third as prevalent as schizophrenia; schizoaffective disorder bipolar type more common in young adults, schizoaffective disorder depressive type more common in older adults
- depressive symptoms correlated with higher suicide risk

### Treatment
- antipsychotics, mood stabilizers, and antidepressants

### Prognosis
- between that of schizophrenia and of mood disorder

## Delusional Disorder

### DSM-5 DIAGNOSTIC CRITERIA FOR DELUSIONAL DISORDER
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A. the presence of one (or more) delusions with a duration of 1 mo or longer
B. criterion A for schizophrenia has never been met
   Note: hallucinations, if present, are not prominent and are related to the delusional theme
C. apart from the impact of the delusion(s) or its ramifications, functioning is not markedly impaired, and behaviour is not obviously bizarre or odd
D. if manic or major depressive episodes have occurred, these have been brief relative to the duration of the delusional periods
E. the disturbance is not attributable to the physiological effects of a substance or another medical condition and is not better explained by another mental disorder

- **subtypes**: erotomanic, grandiose, jealous, persecutory, somatic, mixed, unspecified
- **further specify**: bizarre content, type of episode (i.e. first episode, multiple episode), severity

### Treatment
- antipsychotics, psychotherapy, and antidepressants

### Prognosis
- may respond well to antipsychotics but most patients refuse them and have chronic, unremitting course; some maintain a high level of functioning; some progress to schizophrenia

# Mood Disorders

### Definitions
- accurate diagnosis of a mood disorder requires a careful past medical and psychiatric history to detect past mood episodes and to rule out whether these episodes were secondary to substance use, a medical condition, etc
- mood episodes represent a combination of symptoms comprising a predominant mood state that is abnormal in quality or duration (i.e. major depressive, manic, mixed, hypomanic). DSM-5 Criteria for mood episodes are listed below
- types of mood disorders include:
  - depressive (major depressive disorder, persistent depressive disorder)
  - bipolar (bipolar I/II disorder, cyclothymia)
  - induced by or due to ("secondary to") a general medical condition, substance, medication, other psychiatric condition

### Medical Workup of Mood Disorder
- routine screening: physical exam, CBC, extended electrolytes, renal, liver and thyroid function tests, drug screen, medications list
- additional screening: B12 (in older people), neurological consultation, chest X-ray, ECG, head imaging

## Mood Episodes

### DSM-5 DIAGNOSTIC CRITERIA FOR MAJOR DEPRESSIVE EPISODE
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A. ≥5 of the following symptoms have been present during the same 2 wk period and represent a change from previous functioning; at least one of the symptoms is either 1) depressed mood or 2) loss of interest or pleasure (anhedonia)
   **Note**: do not include symptoms that are clearly attributable to another medical condition
   - depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others
   - markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
   - significant and unintentional weight loss/weight gain, or decrease/increase in appetite nearly every day
   - insomnia or hypersomnia nearly every day



**Criteria for Depression (≥5)**

**MSIGECAPS**
**M**ood: depressed
**S**leep: increased/decreased
**I**nterest: decreased
**G**uilt
**E**nergy: decreased
**C**oncentration: decreased
**A**ppetite: increased/decreased
**P**sychomotor: agitation/retardation
**S**uicidal ideation

- psychomotor agitation or retardation nearly every day
- fatigue or loss of energy nearly every day
- feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
- diminished ability to think or concentrate, or indecisiveness, nearly every day
- recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
C. the episode is not attributable to the direct physiological effects of a substance or a GMC

## DSM-5 CRITERIA FOR MANIC EPISODE

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A. a distinct period of abnormally and persistently elevated, expansive, or irritable mood, and abnormally and persistently increased goal-directed activity or energy, lasting ≥1 wk and present most of the day, nearly every day (or any duration if hospitalization is necessary)
B. during the period of mood disturbance and increased energy or activity, ≥3 of the following symptoms have persisted (4 if the mood is only irritable) have been present to a significant degree and represent a noticeable change from usual behaviour
   - inflated self-esteem or grandiosity
   - decreased need for sleep (i.e. feels rested after only 3 h of sleep)
   - more talkative than usual or pressure to keep talking
   - flight of ideas or subjective experience that thoughts are racing
   - distractibility (i.e. attention too easily drawn to unimportant or irrelevant external stimuli)
   - increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
   - excessive involvement in pleasurable activities that have a high potential for painful consequences (i.e. engaging in unrestrained shopping sprees, sexual indiscretions, or foolish business investments)
C. the mood disturbance is sufficiently severe to cause marked impairment in social/occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features
D. the episode is not attributable to the physiological effects of a substance or another medical condition

Note: A full manic episode that emerges during antidepressant treatment but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode, and therefore, a bipolar I diagnosis

Note: Criteria A-D constitute a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder



**Criteria for Mania (≥3)**

**GST PAID**
**G**randiosity
**S**leep (decreased need)
**T**alkative
**P**leasurable activities, Painful consequences
**A**ctivity
**I**deas (flight of)
**D**istractible

### Hypomanic Episode

- criterion A and B of a manic episode is met, but duration is ≥4 d
- episode associated with an uncharacteristic change in functioning that is observable by others but not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization
- absence of psychotic features (if these are present the episode is, by definition, manic)

### Mixed Features

- an episode specifier in bipolar or depression that indicates the presence of both depressive and manic symptoms concurrently, classified by the disorder and primary mood episode component (i.e. bipolar disorder, current episode manic, with mixed features)
- clinical importance due to increased suicide risk and appropriate treatment
- if found in patient diagnosed with major depression, high index of suspicion for bipolar disorder
- while meeting the full criteria for a major depressive episode, the patient has on most days ≥3 of criteria B for a manic episode
- while meeting the full criteria for a manic/hypomanic episode, the patient has on most days ≥3 of criteria A for a depressive episode (the following criterion A cannot count: psychomotor agitation, insomnia, difficulties concentrating, or weight changes)

# Depressive Disorders

## MAJOR DEPRESSIVE DISORDER

### DSM-5 DIAGNOSTIC CRITERIA FOR MAJOR DEPRESSIVE DISORDER (MDD)

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

A. presence of a MDE
B. the MDE is not better accounted for by schizoaffective disorder and is not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder NOS
C. there has never been a manic episode or a hypomanic episode
**Note**: This exclusion does not apply if all of the manic-like, or hypomanic-like episodes are substance or treatment-induced or are due to the direct physiological effects of another medical condition

- **specifiers**: with anxious distress, mixed features, melancholic features, atypical features, mood-congruent psychotic features, mood-incongruent psychotic features, catatonia, peripartum onset, seasonal pattern
- single vs. recurrent is an episode descriptor that carries prognostic significance. Recurrent is classified as the patient having two or more distinct MDE episodes; to be considered separate the patient must have gone 2 consecutive months without meeting criteria

### Epidemiology

- lifetime prevalence: 12%
- peak prevalence age 15-25 yr (M:F = 1:2)

### Etiology

- biological
  - genetic: 65-75% MZ twins; 14-19% DZ twins, 2-4 fold increased risk in first-degree relatives
  - neurotransmitter dysfunction: decreased activity of 5-HT, NE, and DA at neuronal synapse; changes in GABA and glutamate; various changes detectable by fMRI
  - neuroendocrine dysfunction: abnormal HPA axis activity
  - neuroanatomy and neurophysiology: decreased hippocampal volume, increased size of ventricles; decreased REM latency and slow-wave sleep; increased REM length
  - immunologic: increased pro-inflammatory cytokines IL-6 and TNF
  - secondary to medical condition, medication, substance use disorder
- psychosocial
  - cognitive (i.e. distorted schemata, Beck's cognitive triad: negative views of the self, the world, and the future)
  - environmental factors (i.e. job loss, bereavement, history of abuse or neglect, early life adversity)
  - comorbid psychiatric diagnoses (i.e. anxiety, substance abuse, developmental disability, dementia, eating disorder)

### Risk Factors

- sex: F>M, 2:1
- family history: depression, alcohol abuse, suicide attempt or completion
- childhood experiences: loss of parent before age 11, negative home environment (abuse, neglect)
- personality: neuroticism, insecure, dependent, obsessional
- recent stressors: illness, financial, legal, relational, academic
- lack of intimate, confiding relationships or social isolation
- low socioeconomic status

### Clinically-Significant Depressive Symptoms in the Elderly

- affects about 15% of community residents >65 yr old; up to 50% in nursing homes
- high suicide risk due to social isolation, chronic medical illness, decreased independence
- suicide peak: males aged 80-90; females aged 50-65
- low mood or dysphoria may not be a reliable indicator of depression in those >70 yr
- often present with somatic complaints (i.e. changes in weight, sleep, energy; chronic pain) or anxiety symptoms
- may have prominent cognitive changes after onset of mood symptoms (dementia syndrome of depression)
- see Table 3, for a comparison of delirium and dementia

### Treatment

- lifestyle: increased aerobic exercise, mindfulness-based stress reduction
- biological: SSRIs, SNRIs, other antidepressants, somatic therapies (see *Pharmacotherapy*, PS44, and *Somatic Therapies*, PS52)
  - 1st line pharmacotherapy: sertraline, escitalopram, venlafaxine, mirtazapine
  - for partial response, optimize the dose or add augmenting agent (bupropion, quetiapine-XR, aripiprazole, lithium)
  - for non-response, change class of antidepressant
  - typical response to antidepressant treatment: physical symptoms improve at 2 wk, mood/cognition by 4 wk; if no improvement after 4 wk at the highest tolerated therapeutic dosage, alter regimen

**Antidepressants for Depression in Physical Medical Illness**
Cochrane Database Syst Rev 2000;(4):CD001312
**Purpose**: To evaluate whether antidepressants are clinically effective and acceptable for treatment of depression in patients who also have a physical illness.
**Methods**: Systematic review of RCTs comparing any antidepressant drug as defined by the British National Formulary with placebo or no treatment, in patients aged 16 years and over who have been formally diagnosed with depression by any criterion, and have a specified physical disorder. Main outcome measures were number of individuals demonstrating improvement or recovery by the end of the trial, and number completing treatment (as a proxy for treatment acceptability).
**Results**: Eighteen studies with 838 patients having varied physical illnesses were included. Patients treated with antidepressants were significantly more likely to improve than those given placebo (13 studies, OR 0.37, 95% CI 0.27-0.51) or no treatment (1 study, OR 3.45, 11.1-1.10) (number needed to treat relative to placebo = 4.2, 3.2-6.4). Most antidepressants were associated with a small but significant increase in dropouts (OR 1.66, 1.14-2.40; NNH 9.8, 5.4-42.9). Among two studies evaluating impact on function and quality of life, drug was found to be better than no treatment for HIV patients, and drug was not significantly different than placebo in lung disease patients. Tricyclics appeared to be more effective than SSRIs but also more likely to produce dropouts, based on non-randomized comparisons between trials.
**Conclusion**: Antidepressants cause improvements in depression in patients with various physical diseases significantly more frequently than placebo or no treatment. Antidepressants were reasonably acceptable to patients. Tricyclics may be more effective than SSRIs but may also produce more dropouts. As such, antidepressants should at least be considered in those with concomitant physical illness and depression.

  - ECT: currently fastest and most effective treatment for MDD. Consider in severe, psychotic or treatment-resistant cases
  - rTMS: current data support efficacy equivalent to medications (but not to ECT) with good safety and tolerability
  - phototherapy: especially if seasonal component, shift work, sleep dysregulation
- psychological
  - individual therapy (CBT, interpersonal, supportive), group therapy, family therapy
- social: vocational rehabilitation, social skills training
- experimental: magnetic seizure therapy, deep brain stimulation, ketamine

### Prognosis
- one year after diagnosis of MDD without treatment: 40% of individuals still have symptoms that are sufficiently severe to meet criteria for MDD, 20% continue to have some symptoms that no longer meet criteria for MDD, 40% have no symptoms

## PERSISTENT DEPRESSIVE DISORDER

## DSM-5 DIAGNOSTIC CRITERIA FOR PERSISTENT DEPRESSIVE DISORDER
**Note**: in DSM-IV-TR this was referred to as Dysthymia

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

A. depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for ≥2 yr
   Note: in children and adolescents, mood can be irritable and duration must be at least 1 yr
B. presence, while depressed, of ≥2 of the following:
   - poor appetite or overeating
   - insomnia or hypersomnia
   - low energy or fatigue
   - low self-esteem
   - poor concentration or difficulty making decisions
   - feelings of hopelessness
C. during the 2 yr period (1 yr for children or adolescents) of the disturbance, the person has never been without the symptoms in criteria A and B for more than 2 mo at a time
D. criteria for a major depressive disorder may be continuously present for 2 yr
E. there has never been a manic episode or a hypomanic episode, and criteria have never been met for cyclothymic disorder
F. the disturbance is not better explained by a persistent schizoaffective disorder, schizophrenia, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder
G. the symptoms are not due to the direct physiological effects of a substance or another medical condition
H. the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

- **specifiers**:
  - with anxious distress, mixed features, melancholic features, atypical features, mood-congruent psychotic features, mood-incongruent psychotic features, catatonia, peri-partum onset, seasonal pattern
  - partial remission, full remission
  - early onset <21 yr of age), late onset (>21 yr of age)
  - with pure dysthymic syndrome (full criteria for MDE have not been met in at least preceding 2 yr), with persistent MDE (full criteria for MDE have been met throughout preceding 2 yr)
  - •with intermittent MDEs, with current episode: full criteria for a MDE are currently met, but there have been periods of at least 8 weeks in at least the preceding 2 years with symptoms below the threshold for a full MDE
  - with intermittent MDEs, without current episode: full criteria for a MDE are not currently met, but there has been one or more major depressive episodes in at least the preceding 2 years.
  - specify current severity: mild, moderate, severe

### Epidemiology
- lifetime prevalence: 2-3%; M=F

### Treatment
- psychological
  - traditionally, psychotherapy was the principal treatment for persistent depressive disorder; recent evidence suggests some (but generally inferior) benefit for pharmacological treatment. Combinations of the two may be most efficacious
- biological
  - antidepressant therapy: SSRIs (i.e. sertraline, escitalopram), TCAs (i.e. nortiptyline)

# Postpartum Mood Disorders

### Postpartum "Blues"
- transient period of mild depression, mood instability, anxiety, decreased concentration; considered to be normal in response to fluctuating hormonal levels, the stress of childbirth, and the increased responsibilities of motherhood
- occurs in 50-80% of mothers; begins 2-4 d postpartum, usually lasts 48 h, can last up to 10 d
- does not require psychotropic medication
- usually mild or absent: feelings of inadequacy, anhedonia, thoughts of harming baby, suicidal thoughts

### MAJOR DEPRESSIVE DISORDER WITH PERIPARTUM ONSET (POSTPARTUM DEPRESSION)

### Clinical Feature
- MDD with onset during pregnancy or within 4 wk following delivery
- typically lasts 2-6 mo; residual symptoms can last up to 1 yr
- may present with psychosis (rare, 0.2% – more frequent with post-partum mania)
- severe symptoms may include complete disinterest in baby, suicidal and infanticidal ideation

### Epidemiology
- occurs in up to 10% of mothers, risk of recurrence 50%

### Risk Factors
- previous history of a mood disorder (postpartum or otherwise), family history of mood disorder
- psychosocial factors: stressful life events, unemployment, marital conflict, lack of social support, unwanted pregnancy, colicky or sick infant

### Treatment
- psychotherapy (CBT or IPT)
- short-term safety of maternal SSRIs for breastfeeding infants established; long-term effects unknown
- if depression severe or psychotic symptoms present, consider ECT

### Prognosis
- impact on child development: increased risk of cognitive delay, insecure attachment, behavioural disorders
- treatment of mother improves outcome for child at 8 mo through increased mother-child interaction

**Selective Serotonin Reuptake Inhibitors in Pregnancy and Infant Outcomes**
Paediatr Child Health 2011;16:562-563
Canadian Pediatric Society (CPS) clinical practice guideline recommendations: It is important to treat depression in pregnancy. There is no evidence that SSRIs increase the risk of major malformations. There is conflicting evidence concerning the association of paroxetine and cardiac malformations. SSRIs are not contraindicated while breast-feeding.

**Antidepressant Use in Pregnancy and the Risk of Cardiac Defects**
N Engl J Med. 2014 Jun 19;370(25):2397-407
**Background**: It is uncertain whether selective serotonin-reuptake inhibitors (SSRIs) and other antidepressants during pregnancy is associated increased risk of congenital cardiac defects. There are concerns about an association between paroxetine use and right ventricular outflow tract obstruction and between sertraline use and ventricular septal defects.
**Methods**: Cohort study including 949,504 women enrolled in Medicaid for a 7 year period. The risk of major cardiac defects among infants born to women who took antidepressants during the 1st trimester was compared with the risk among infants born to women who did not use antidepressants. An unadjusted analysis was used, possible confounders considered.
**Results**: Overall, the chance of infants not exposed to antidepressants born with a cardiac defect was 72.3 per 10,000 infants, and infants with exposure was 90.1 per 10,000 infants. The relative risks of any cardiac defect with the use of SSRIs were 1.06 (95% CI, 0.93 to 1.22) in the fully adjusted analysis restricted to women with depression. No significant association was found between the use of paroxetine and right ventricular outflow tract obstruction (RR, 1.07) or between the use of sertraline and ventricular septal defects (RR, 1.04).
**Conclusions**: No substantial increase in risk of cardiac malformations attributable to antidepressant use during the 1st trimester.

# Bipolar Disorders

### BIPOLAR I / BIPOLAR II DISORDER

### Definition
- Bipolar I Disorder
  - disorder in which at least one manic episode has occurred
  - if manic symptoms lead to hospitalization, or if there are psychotic symptoms, the diagnosis is BP I
  - commonly accompanied by at least 1 MDE but not required for diagnosis
  - time spent in mood episodes: 53% asymptomatic, 32% depressed, 9% cycling/mixed, 6% hypo/manic
- Bipolar II Disorder
  - disorder in which there is at least 1 MDE, 1 hypomanic episode, and no manic episodes
  - while hypomania is less severe than mania, Bipolar II is not a "milder" form of Bipolar I
  - time spent in mood episodes: 46% asymptomatic, 50% depressed, 1% cycling/mixed, 2% hypo/manic
  - Bipolar II is often missed due to the severity and chronicity of depressive episodes and low rates of spontaneous reporting and recognition of hypomanic episodes

Bipolar II is quite often missed and many patients are symptomatic for up to a decade before accurate diagnosis and treatment

### Classification
- classification of bipolar disorder involves describing the disorder (I or II) and the current or most recent mood episode as either manic, hypomanic, or depressed
- specifiers: with anxious distress, depressed with mixed features, hypo/manic with mixed features, melancholic features, atypical features, mood-congruent or -incongruent psychotic features, catatonia, peripartum onset, seasonal pattern, rapid cycling (4+ mood episodes in 1 yr)

### Epidemiology
- lifetime prevalence: 1% BD I, 1.1% BD II, 2.4% Subthreshold BD; M:F = 1:1
- age of onset: teens to 20s, usually MDE first, manic episode 6-10 years after, average age of first manic episode:32 yr

Patients with bipolar disorder are at higher risk for suicide when they switch from mania to depression, especially as they become aware of consequences of their behaviour during the manic episode

### Risk Factors
- genetic: 60-65% of bipolar patients have family history of a major mood disorder, especially bipolar disorder
- clinical features of MDE history favouring bipolar over unipolar diagnosis: early age of onset (<25 yr), increased number of MDEs, psychotic symptoms, postpartum onset, anxiety disorders (especially separation, panic), antidepressant failure due to early "poop out" or hypomanic symptoms, early impulsivity and aggression, substance abuse, cyclothymic temperament

### Treatment
- lifestyle: psychoeducation regarding cycling nature of illness, ensure regular check ins, develop early warning system, "emergency plan" for manic episodes, promote stable routine (sleep, meals, exercise)
- biological: lithium, anticonvulsants, antipsychotics, ECT (if resistant); monotherapy with antidepressants should be avoided
  - mood stabilizers vary in their ability to "treat" (reduce symptoms acutely) or "stabilize" (prevent relapse and recurrence) manic and depressive symptoms; multi-agent therapy is common
  - treating mania: lithium, divalproex, carbamazepine (2nd line), SGA, ECT, benzodiazepines (for acute agitation)
  - preventing mania: same as above but usually at lower dosages, minus ECT and benzodiazepines
  - treating depression: lithium, lurasidone, quetiapine, lamotrigine, antidepressants (only with mood stabilizer), ECT
  - preventing depression: same as above plus aripiprazole, divalproex (note: quetiapine first line in treating bipolar II depression)
  - mixed episode or rapid cycling: multi-agent therapy: lithium or divalproex + SGA (lurasidone, aripiprazole)
- **psychological**: supportive psychotherapy, CBT, IPT or interpersonal social rhythm therapy, family therapy
- **social**: vocational rehabilitation, consider leave of absence from school/work, assess capacity to manage finances, drug and EtOH cessation, sleep hygiene, social skills training, recruitment and education of family members

### Course and Prognosis
- high suicide rate (15% mortality from suicide), especially in mixed states
- BD I and II are chronic conditions with a relapsing and remitting course featuring alternating manic and depressive episodes; depressive symptoms tend to occur more frequently and last longer than manic symptoms
- can achieve high level of functioning between episodes
- may switch rapidly between depression and mania without any period of euthymia in between
- high recurrence rate for mania – 90% will have a subsequent episode in the next 5 yr
- long term follow-up of BD I – 15% well, 45% well with relapses, 30% partial remission, 10% chronically ill

## CYCLOTHYMIA
Adapted/summarized from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

### Diagnosis
- presence of numerous periods of hypomanic and depressive symptoms (not meeting criteria for full hypomanic episode or MDE) for ≥2 yr; never without symptoms for >2 mo
- never have met criteria for MDE, manic or hypomanic episodes
  - symptoms not better explained by any psychotic disorder (including schizoaffective, schizophrenia, schizophreniform, delusional disorder, or other specified/unspecified)
- symptoms are not due to the direct physiological effects of a substance or GMC
- symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

### Treatment
- similar to Bipolar I: mood stabilizer ± psychotherapy, avoid antidepressant monotherapy, treat any comorbid substance use disorder



Lithium is among few agents with proven efficacy in preventing suicide attempts and completions



Monotherapy with antidepressants should be avoided in patients with bipolar depression as patients can switch from depression into mania



**The 4 L's for Bipolar Depression**
**L**ithium, **L**amotrigine, **L**urasidone, Seroque**L**



**A Randomized Controlled Trial of Cognitive Therapy for Bipolar Disorder: Focus on Long-Term Change**
J Clin Psychiatry 2006;67:277-286
**Purpose**: To evaluate long-term change with cognitive therapy plus emotive techniques for the treatment of bipolar disorder.
**Methods**: Blinded RCT including patients with DSM-IV bipolar I or II disorder allocated to either a 6 mo trial of cognitive therapy (CT) with emotive techniques or treatment as usual. Both groups received mood stabilizers. Main outcomes were relapse rates, dysfunctional attitudes, psychosocial functioning, hopelessness, self-control, and medication adherence. Patients were assessed by independent raters blinded to treatment group.
**Results**: At 6 mo, CT patients experienced fewer depressive symptoms and fewer dysfunctional attitudes. There was a non-significant (p=0.06) trend to greater time to depressive relapse. At 12 mo follow-up, CT patients had lower Young Mania Rating scores and improved behavioural self-control. At 18 mo, CT patients reported less severity of illness.
**Conclusions**: CT appears to provide benefits in the 12 mo after completion of therapy.

# Anxiety Disorders

## Definition

- anxiety is a universal human experience which can serve as an adaptive mechanism to facilitate appropriate reactions to external threat
- anxiety becomes pathological when:
  - fear is greatly out of proportion to risk/severity of threat
  - response continues beyond existence of threat or becomes generalized to other similar or dissimilar situations
  - social or occupational functioning is impaired
  - often comorbid with substance use and depression
- manifestations of anxiety are a result of the activation of the sympathetic nervous system and can be described through;
  - physiology: main brain structure involved is the amygdala ; neurotransmitters involved include 5-HT, cholecystokinin, epinephrine, norepinephrine, and DA
  - psychology: one's thoughts about a given situation or stimulus contribute to the feeling of fear and perception of threat
  - behaviour: anxiety can lead to avoidance which can result in disruption to daily functioning.

## Differential Diagnosis

**Table 2. Differential Diagnosis of Anxiety Disorders**

| | |
|---|---|
| **Cardiovascular** | Post-MI, arrhythmia, congestive heart failure, pulmonary embolus, mitral valve prolapse |
| **Respiratory** | Asthma, COPD, pneumonia |
| **Endocrine** | Hyperthyroidism, pheochromocytoma, hypoglycemia, hyperadrenalism, hyperparathyroidism |
| **Metabolic** | Vitamin B12 deficiency, folate deficiency, porphyria, hypoxemia, hypercalcemia |
| **Neurologic** | Neoplasm, vestibular dysfunction, encephalitis, trauma (contusion or hematoma), MS, temporal lobe epilepsy |
| **Infectious** | Cerebral (meningitis, HIV, syphilis) or systemic |
| **GI** | Gastritis, esophageal spasm |
| **Substance-Induced** | Intoxication (caffeine, amphetamines, cocaine, thyroid replacement, OTC for colds/decongestants), withdrawal (benzodiazepines, alcohol) |

## Medical Workup of Anxiety Disorder

- routine screening: physical exam, CBC, electrolytes, thyroid function test, ECG
- additional screening: extended electrolytes, vitaminB12, folate, chest x-ray, head imaging, neurological consultation, any other tests as per DDx in Table 2

## Risk Factors for the Development of Anxiety Disorders

- biological
  - endocrine disorders (i.e. hyperthyroidism), respiratory conditions (i.e. asthma), CNS conditions (i.e. temporal lobe epilepsy), substances/medications (i.e. excessive stimulant use), chronic medical illness
  - family history
  - personal history of anxiety or mood disorder
  - XX>XY chromosomes
- psychological
  - current stress early childhood trauma, early parental loss

# Panic Disorder

## DSM-5 DIAGNOSTIC CRITERIA FOR PANIC DISORDER

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

A. recurrent unexpected panic attacks – a panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and during which time four (or more) of the following symptoms occur
  - palpitations, pounding heart, or accelerated heart rate
  - sweating
  - trembling or shaking
  - sensations of shortness of breath or smothering
  - feelings of choking
  - chest pain or discomfort
  - nausea or abdominal distress
  - feeling dizzy, unsteady, light-headed, or faint
  - chills or heat sensations
  - paresthesias (numbness or tingling sensations)
  - derealization (feelings of unreality) or depersonalization (being detached from oneself)

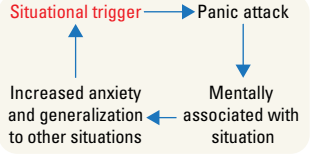



**Figure 2. Mechanism of panic attacks**

- fear of losing control or "going crazy"
- fear of dying

B. 1 mo (or more) of "anxiety about panic attacks" - at least one of the attacks has been followed by one or both of the following:
   - persistent concern or worry about additional panic attacks or their consequences
   - a significant maladaptive change in behaviour related to the attacks
C. the disturbance is not attributable to the physiological effects of a substance or another medical condition
D. the disturbance is not better explained by another mental disorder

### Epidemiology
- lifetime prevalence: 5% (one of the top five most common reasons to see a family doctor); M:F = 1:2-3
- onset: average early-mid 20s, familial pattern

### Treatment
- psychological
  - CBT: interoceptive exposure (deliberate exposure to unpleasant sensations of arousal associated with a panic attack for experiential disconfirmation of their fears); cognitive restructuring (addressing underlying beliefs regarding the panic attacks), relaxation techniques (visualization, box-breathing), psychoeducation
- pharmacological (first line agents)
  - SSRIs: fluoxetine, citalopram, escitalopram, paroxetine, sertraline, fluvoxamine
  - SNRI: venlafaxine XR
  - with SSRI/SNRIs, start with low doses, titrate up as tolerated
  - anxiety disorders often require treatment at higher doses for a longer period of time than depression (i.e. full response may take up to 12 wk)
  - treat for up to 1 year after symptoms resolve to avoid relapse
  - explain expected adverse effects prior to initiation of therapy to prevent non-adherence
  - other antidepressants (mirtazapine, MAOIs)
  - benzodiazepines considered 2nd line (short-term, lowest effective dose, helpful while titrating antidepressant)

### Prognosis
- 6-10 yr post-treatment: 30% well, 40-50% improved, 20-30% no change or worse
- clinical course: chronic, but episodic with psychosocial stressors

**Criteria for Panic Disorder (≥4)**

**STUDENTS FEAR the 3 Cs**
**S**weating
**T**rembling
**U**nsteadiness, dizziness
**D**epersonalization, **D**erealization
**E**xcessive heart rate, palpitations
**N**ausea
**T**ingling
**S**hortness of breath
**Fear** of dying, losing control, going crazy
**3 Cs**: **C**hest pain, **C**hills, **C**hoking

**Panic Attack vs. Panic Disorder**
Panic disorder consists of panic attacks + other criteria

Panic attacks can occur in the context of many different disorders

**Starting Medication for Anxiety**
Start low, go slow, aim high and explain symptoms to expect prior to initiation of therapy to prevent non-adherence due to side effects

# Agoraphobia

### DSM-5 DIAGNOSTIC CRITERIA FOR AGORAPHOBIA
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

A. marked fear or anxiety about two (or more) of the following five situations:
   - using public transportation
   - being in open spaces
   - being in enclosed places
   - standing in line or being in a crowd
   - being outside of the home alone
B. the individual fears or avoids these situations because of thoughts that escape might be difficult or help might not be available in the event of developing panic-like symptoms or other incapacitating or embarrassing symptoms
C. the agoraphobic situations almost always provoke fear or anxiety
D. the agoraphobic situations are actively avoided, require the presence of a companion, or are endured with intense fear or anxiety
E. the fear or anxiety is out of proportion to the actual danger posed by the agoraphobic situations and to the sociocultural context
F. the fear, anxiety, or avoidance is persistent, typically lasting ≥6 mo
G. the fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
H. if another medical condition is present, the fear, anxiety, or avoidance is clearly excessive
I. the fear, anxiety, or avoidance is not better explained by the symptoms of another mental disorder and are not related exclusively to obsessions, perceived defects or flaws in physical appearance, reminders of traumatic events, or fear of separation

**Note**: agoraphobia is diagnosed irrespective of the presence of panic disorder. If an individual's presentation meets criteria for panic disorder and agoraphobia, both diagnoses should be assigned

### Treatment
- as per specific panic disorder

# Generalized Anxiety Disorder

**Criteria for GAD (≥3)**

**C-FIRST**
**C**oncentration issues
**F**atigue
**I**rritability
**R**estlessness
**S**leep disturbance
**T**ension (muscle)

## DSM-5 DIAGNOSTIC CRITERIA FOR GENERALIZED ANXIETY DISORDER

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

A. excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 mo, about a number of events or activities (i.e. work or school performance)
B. the individual finds it difficult to control the worry
C. the anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 mo)
    1. restlessness or feeling keyed up or on edge
    2. being easily fatigued
    3. difficulty concentrating or mind going blank
    4. irritability
    5. muscle tension
    6. sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep)
D. the anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
E. the disturbance is not attributable to the physiological effects of a substance or another medical condition
F. the disturbance is not better explained by another mental disorder

### Epidemiology

- 1 yr prevalence: 1-4%, lifetime prevalence 6%; M:F = 1:2
    - 8% of all who seek primary care treatment (WHO)
- bimodal age of onset: before 20 or middle adulthood

Source: Depression and other common mental disorders: Global health estimates. Geneva: World Health Organization, 2017.

### Treatment

- lifestyle: avoid caffeine and EtOH, sleep hygiene
- psychological: CBT (cognitive restructuring), relaxation techniques, mindfulness
- biological
    - 1st line SSRIs (escitalopram, sertraline, paroxetine), SNRIs (venlafaxine XR, duloxetine), pregabalin
    - benzodiazepines considered 2nd line (short-term, lowest effective dose, helpful while titrating antidepressant)
    - β-blockers not recommended

### Prognosis

- rarely abates over time
- depends on pre-morbid personality functioning, stability of relationships, work, and severity of environmental stress

# Phobic Disorders

Adopted/summarized from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

### Specific Phobia

- definition: marked and persistent (>6 mo) fear that is excessive or unreasonable, cued by presence or anticipation of a specific object or situation
- lifetime prevalence 12-16%; M:F ratio variable
- types: animal/insect, environment (heights, storms), blood/injection/injury, situational (airplane, closed spaces), other (loud noise, clowns)

### Social Phobia (Social Anxiety Disorder)

- definition: marked and persistent (>6 mo) fear of social or performance situations in which one is exposed to unfamiliar people or to possible scrutiny by others; fearing he/she will act in a way that may be humiliating or embarrassing (i.e. public speaking, initiating or maintaining conversation, dating, eating in public)
- 12 mo prevalence rate may be as high as 7%; M:F ratio approximately equal

### Diagnostic Criteria for Phobic Disorders

- exposure to stimulus almost invariably provokes an immediate anxiety response; may present as a panic attack
- person recognizes fear as excessive or unreasonable
- situations are avoided or endured with anxiety/distress
- significant interference with daily routine, occupational/social functioning, and/or marked distress

### Treatment

- psychological
    - cognitive behaviour therapy (focusing on both in vivo and virtual exposure therapy, gradually facing feared situations)
    - behavioural therapy is more efficacious than medication for specific phobia
- biological treatment for social anxiety disorder
    - first line: SSRIs (escitalopram, sertraline, fluvoxamine, paroxetine) SNRI (venlafaxine XR), pregabalin

# Obsessive-Compulsive and Related Disorders

## Obsessive-Compulsive Disorder

### DSM-5 DIAGNOSTIC CRITERIA FOR OBSESSIVE-COMPULSIVE DISORDER

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

A. presence of obsessions, compulsions, or both
- obsessions are defined by (1) and (2)
  1. recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted, and cause marked anxiety or distress in most individuals
  2. the individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action (i.e. by performing a compulsion; see below)
- compulsions are defined by (1) and (2)
  1. repetitive behaviours (i.e. hand washing, ordering, checking) or mental acts (i.e. praying, counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly
  2. behaviours mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviours or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive

B. the obsessions or compulsions are time-consuming (i.e. take >1 h/d) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

C. the obsessive-compulsive symptoms are not attributable to the physiological effects of a substance or another medical condition

D. the disturbance is not better explained by the symptoms of another mental disorder

- **specifiers**: with good or fair insight, with poor insight, with absent insight/delusional beliefs, tic-related

### Epidemiology

- 12 mo prevalence 1.1-1.8%; females affected at slightly higher rates than males
- rate of OCD in first-degree relatives is higher than in the general population
- common comorbidities: anxiety disorders, depression, obsessive-compulsive PD, tic disorders, body dysmorphic disorder, trichotillomania, and excoriation disorder

### Risk Factors

- genetic: neurological dysfunction, family history
- environmental: adverse childhood experiences (i.e. abuse, behavioural inhibition), exposure to traumatic events, group A streptococcal infection

### Treatment

- CBT: exposure with response prevention (ERP) – involves exposure to feared situations with the addition of preventing the compulsive behaviours; cognitive strategies include challenging underlying beliefs
- pharmacotherapy: SSRIs/SNRIs (12-16 week trials, higher therapeutic dosages than used for depression), clomipramine; adjunctive antipsychotics (risperidone)

### Prognosis

- may be refractory and chronic

## Related Disorders

### Body Dysmorphic Disorder

- preoccupation with ≥1 perceived flaws in physical appearance not observed by others
- repetitive behaviours (i.e. mirror checking, excessive grooming, skin picking, or reassurance seeking) or mental acts (i.e. comparing self to others) related to appearance
- ± muscle dysmorphia
- causes clinically significant distress or functional impairment
- rule out eating disorder

### Hoarding Disorder

- persistent difficulty discarding possessions regardless of actual value
- feels the need to save items, discarding creates distress
- results in possessions cluttering/compromising active living areas (may be uncluttered with 3rd party intervention, i.e. family member, cleaners, authorities)
- causes clinically significant distress or functional impairment
- rule out brain injury, cerebrovascular disease, Prader-Willi syndrome, OCD, MDD (low energy), psychotic disorder (delusions), neurocognitive disorder, ASD (restricted interests)

### Trichotillomania (Hair-Pulling Disorder)
- recurrent pulling out own hair resulting in hair loss
- repeated attempts to stop or decrease hair pulling
- causes clinically significant distress or functional impairment
- rule out dermatological condition, body dysmorphic disorder

### Excoriation (Skin-Picking) Disorder
- recurrent skin picking resulting in lesions
- repeated attempts to stop or decrease skin picking
- causes clinically significant distress or functional impairment
- rule out scabies, substance use (i.e. cocaine), psychotic disorder (delusions, tactile hallucinations), body dysmorphic disorder, stereotypic movement disorder, non-suicidal self-injury

# Trauma- and Stressor-Related Disorders

## Post-Traumatic Stress Disorder

### DSM-5 DIAGNOSTIC CRITERIA FOR POST-TRAUMATIC STRESS DISORDER
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association.

A. exposure to actual or threatened death, serious injury, or sexual violence in ≥1 of the following ways:
- directly experiencing the traumatic event(s)
- witnessing, in person, the event(s) as it occurred to others
- learning that the traumatic event(s) occurred to a close family member or close friend; in cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental
- experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (i.e. first responders collecting human remains, police officers repeatedly exposed to details of child abuse)

B. presence of ≥1 of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:
- recurrent, involuntary, and intrusive distressing memories of the traumatic event(s)
- recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s)
- dissociative reactions (i.e. flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring
- intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s)
- marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s)

C. persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:
- avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s)
- avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s)

D. negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by ≥2 of the following:
- inability to remember an important aspect of the traumatic event(s)
- persistent and exaggerated negative beliefs or expectations about oneself, others, or the world
- persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others
- persistent negative emotional state (i.e. fear, horror, anger, guilt, or shame)
- markedly diminished interest or participation in significant activities
- feelings of detachment or estrangement from others
- persistent inability to experience positive emotions

E. marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by ≥2 of the following:
- irritable behaviour and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects
- reckless or self-destructive behaviour
- hypervigilance
- exaggerated startle response
- problems with concentration
- sleep disturbance (i.e. difficulty falling or staying asleep or restless sleep)

F. duration of the disturbance (criteria B, C, D, and E) is more than 1 mo

G. the disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

H. the disturbance is not attributable to the physiological effects of a substance or another medical condition



**Criteria for Post-Traumatic Stress Disorder**

**TRAUMA**
**T**raumatic event
**R**e-experience the event
**A**voidance of stimuli associated with the trauma
**U**nable to function
**M**ore than a **M**onth
**A**rousal increased
+ negative alterations in cognition and mood

- **specifiers**:
  - with dissociative symptoms (not attributable to physiologic effects of a substance or a medical condition)
  - depersonalization: persistent or recurrent experiences of feeling detached from, or as if one were an outside observer of one's mental processes or body
  - derealization: persistent or recurrent experiences of unreality of surroundings
  - with delayed expression: the full diagnostic criteria are not met until 6 mo after the event

### Epidemiology
- lifetime prevalence in Canada is 9%
- 75% have another comorbid psychiatric disorder
- high rates of chronic pain, sleep problems, sexual dysfunction, cognitive dysfunction
- twice as high among women versus men

### Treatment
- trauma therapy, CBT
  - ensure safety and stabilize: emotional regulation techniques (i.e. breathing, relaxation)
  - once coping mechanisms established, can explore/mourn trauma, challenge dysfunctional beliefs, etc.
  - reconnect and integrate: exposure therapy, etc.
- biological
  - first line: fluoxetine, paroxetine, sertraline, venlafaxine XR
  - prazosin (for treating disturbing dreams and nightmares)
  - benzodiazepines (for acute anxiety)
  - adjunctive atypical antipsychotics (risperidone, olanzapine)
- eye movement desensitization and reprocessing (EMDR): an experimental method of reprocessing memories of distressing events by recounting them while using a form of dual attention stimulation such as eye movements, bilateral sound, or bilateral tactile stimulation (its use is controversial because of limited evidence)

### Complications
- substance abuse, relationship difficulties, depression, impaired social and occupational functioning disorders, personality disorders

**Acute Stress Disorder**
- May be a precursor to PTSD
- Similar symptoms to PTSD
- Symptoms persist 3 d after a trauma until 1 mo after the exposure

## Adjustment Disorder

### Definition
- a diagnosis encompassing patients who have difficulty coping with a stressful life event or situation and develop acute, often transient, emotional or behavioural symptoms that resemble less severe versions of other psychiatric conditions

### DSM-5 DIAGNOSTIC CRITERIA FOR ADJUSTMENT DISORDER
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A. the development of emotional or behavioural symptoms in response to an identifiable stressor(s) occurring within 3 mo of the onset of the stressor(s)
B. these symptoms or behaviours are clinically significant as evidenced by either of the following:
   - marked distress that is in excess of what would be expected from exposure to the stressor
   - significant impairment in social or occupational functioning
C. the stress-related disturbance does not meet criteria for another mental disorder and is not merely an exacerbation of a pre-existing mental disorder
D. the symptoms do not represent normal bereavement
E. once the stressor (or its consequences) has terminated, the symptoms do not persist for more than an additional 6 mo

- **specifiers**: with depressed mood, with anxiety, with mixed anxiety/depression, with conduct disturbance, with mixed disturbance of conduct/emotions, unspecified

### Classification
- types of stressors
  - single (i.e. termination of romantic relationship)
  - multiple (i.e. marked business difficulties and marital problems)
  - recurrent (i.e. seasonal business crises)
  - continuous (i.e. living in a crime-ridden neighbourhood)
  - developmental events (i.e. going to school, leaving parental home, getting married, becoming a parent, failing to attain occupational goals, retirement)

### Epidemiology
- F:M 2:1, prevalence 2-8% of the population

### Treatment
- brief psychotherapy: individual or group (particularly useful for patients dealing with unique and specific medical issues; i.e. colostomy or renal dialysis groups), crisis intervention
- biological
  - benzodiazepines may be used for those with significant anxiety symptoms (short-term, low-dose, regular schedule)

# Bereavement

### Clinical Feature

- bereavement is a normal psychological and emotional reaction to a significant loss, also called grief or mourning
- length and characteristics of "normal" bereavement vary between individual cultures
- normal response: protest → searching and acute anguish → despair and detachment → reorganization
- presence of the following symptoms may indicate abnormal grief/presence of MDD
  - guilt about things other than actions taken or not taken by the survivor at the time of death
  - thoughts of death other than the survivor feeling that they would be better off dead or should have died with the deceased person; morbid preoccupation with worthlessness
  - marked psychomotor retardation; prolonged and marked functional impairment
  - hallucinatory experiences other than hearing the voice or transiently seeing the image of the deceased person
  - dysphoria that is pervasive and independent of thoughts or triggers of the deceased, absence of mood reactivity
- after 12 mo, if patient continues to yearn/long for the deceased, experience intense sorrow/emotional pain in response to the death, remain preoccupied with the deceased or with their circumstance of death, then may start to consider a diagnosis of "persistent complex bereavement disorder"
- if a patient meets criteria for MDD, even in the context of a loss or bereavement scenario, they are still diagnosed with MDD

### Treatment

- support and watchful waiting should be first line, as well as education and normalization of the grief process
- screen for increased alcohol, cigarette and drug use
- normal grief should not be treated with antidepressant or antianxiety medications, as it is important to allow the person to experience the whole mourning process to achieve resolution
- psychosocial: grief therapy (individual or group) is indicated for those needing additional support, or experiencing complex grief/bereavement, or significant MDD
- pharmacotherapy: if MDD present, past history of mood disorders, severe symptoms

**Risk Factors for Poor Bereavement Outcome**

- Poor social supports
- Unanticipated death or lack of preparation for death
- Highly dependent relationship with deceased
- High initial distress
- Other concurrent stresses and losses
- Death of a child
- Pre-existing psychiatric disorders, especially depression and separation anxiety

Bereavement is associated with a significant increase in morbidity and mortality acutely following the loss, with effects seen up to 1 yr after

Loneliness is the most common symptom that continues to persist in normal bereavement and may last several years

# Neurocognitive Disorders

## Delirium

- see Neurology, N20

### DSM-5 DIAGNOSTIC CRITERIA FOR DELIRIUM

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

A. attention and awareness: disturbance in attention (i.e. reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment)
B. acute and fluctuating: disturbance develops over short period of time (usually hours to days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day
C. cognitive changes: an additional disturbance in cognition (i.e. memory deficit, disorientation, language, visuospatial ability, or perception)
D. not better explained: disturbances in criteria A and C are not better explained by another neurocognitive disorder (pre-existing, established, or evolving) and do not occur in the context of a severely reduced level of arousal (i.e. coma)
E. direct physiological cause: evidence that disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e. due to a drug of abuse or medication), toxin, or is due to multiple etiologies

- **Note**: delirium can be described as HYPERactive, HYPOactive, or MIXED presentation. While patients with hyperactive delirium may demonstrate features of restlessness and agitation, as well as experience hallucinations and delusions, those with hypoactive delirium present with lethargy, sedation and respond slowly to questioning

### Clinical Feature and Assessment

- common symptoms
  - distractibility, disorientation (time, place, rarely person)
  - misinterpretations, illusions, hallucinations (visual hallucinations are organic until proven otherwise)
  - speech/language disturbances (dysarthria, dysnomia)
  - affective symptoms (anxiety, fear, depression, irritability, anger, euphoria, apathy)
  - shifts in psychomotor activity (groping/picking at clothes, attempts to get out of bed when unsafe, sudden movements, sluggishness, lethargy)
  - impairment in sleep duration and/or architecture (i.e. sleep-wake reversal)
- Folstein Mini Mental Status Exam or Montreal Cognitive Assessment are helpful to assess baseline of altered mental state (i.e. score will improve as symptoms resolve)

**Confusion Assessment Method (CAM) for Diagnosis of Delirium**

Highly sensitive and specific method to diagnose delirium
- Part 1: an assessment instrument that screens for overall cognitive impairment
- Part 2: includes four features found best able to distinguish delirium from other cognitive impairments

Need (1) + (2) + (3 or 4)
(1) Acute onset and fluctuating course
(2) Inattention
(3) Disorganized thinking
(4) Altered level of consciousness - hyperactive or hypoactive

### Risk Factors
- most common precipitating factors include: polypharmacy (particularly involving psychoactive drugs such as anticholinergics), infection, dehydration, immobility, malnutrition, and use of bladder catheters
- other factors include:
  - hospitalization (incidence 10-56%); frail and surgical patients are at the greatest risk
  - previous delirium
  - nursing home residents (incidence 60%)
  - old age (especially males)
  - severe illness (i.e. cancer, AIDS)
  - recent anesthesia or surgery
  - brain vulnerability: pre-existing neurologic or neurocognitive disorder, substance abuse, past psychiatric illness

**Etiology of Delirium**

**I WATCH DEATH**
- **I**nfectious (encephalitis, meningitis, UTI, pneumonia)
- **W**ithdrawal (alcohol, barbiturates, benzodiazepines)
- **A**cute metabolic disorder (electrolyte imbalance, hepatic or renal failure)
- **T**rauma (head injury, post-operative)
- **C**NS pathology (stroke, hemorrhage, tumour, seizure disorder, Parkinson's)
- **H**ypoxia (anemia, cardiac failure, pulmonary embolus)
- **D**eficiencies (vitamin $B_{12}$, folic acid, thiamine)
- **E**ndocrinopathies (thyroid, glucose, parathyroid, adrenal)
- **A**cute vascular (shock, vasculitis, hypertensive encephalopathy)
- **T**oxins: substance use, sedatives, opioids (especially morphine), anesthetics, anticholinergics, anticonvulsants, dopaminergic agents, steroids, insulin, glyburide, antibiotics (especially quinolones), NSAIDs
- **H**eavy metals (arsenic, lead, mercury)

### Investigations
- standard: CBC and differential, electrolytes (including $Ca^{2+}$, $Mg2^{2+}$, and $PO_4^{3-}$), glucose, BUN, Cr, TSH/T4, LFTs, vitamin B12, folate, albumin; urinalysis, urine C&S
- as indicated: ECG (to assess QT interval when considering treatment with an antipsychotic agent), CXR, head CT or MRI, toxicology/heavy metal screen, VDRL, HIV, LP, blood cultures, EEG (typical finding in delirium is generalized slowing, can also be used to rule out underlying seizures or post-ictal states as etiology)
- indications for CT head: focal neurological deficit, acute change in status, anticoagulant use, acute incontinence, gait abnormality, history of cancer
- MRI may be more useful: it can detect or exclude acute or subacute stroke and multifocal inflammatory lesions in patients with negative head CT

### Management
- identify and manage underlying cause
  - identify and treat underlying cause immediately
  - stop all non-essential medications
  - maintain nutrition, hydration, electrolyte balance, and monitor vitals
- optimize the environment
  - environment: quiet, well-lit, near window for cues regarding time of day
  - optimize hearing and vision
  - room near nursing station for closer observation; constant care if patient jumping out of bed, pulling out lines
  - family member present for reassurance and re-orientation
  - frequent orientation: calendar, clock, reminders
  - avoid frequent changes of assigned nursing staff
- pharmacotherapy
  - low dose, high potency antipsychotics: haloperidol has the most evidence and can be given IV or IM; alternatives include risperidone (less sedating), olanzapine (more sedating, can be anticholinergic itself), quetiapine (if EPS sensitive), aripiprazole (does not prolong QTc)
  - benzodiazepines only used in alcohol/substance withdrawal delirium; otherwise, can worsen delirium (antipsychotics are not useful in EtOH or benzodiazepine withdrawal delirium)
  - try to minimize drugs with anticholinergic effects
- physical restraints to maintain safety only if necessary

### Prognosis
- up to 50% 1yr mortality rate after episode of delirium

## Major Neurocognitive Disorder (Dementia)

- see Neurology, N24

### DSM-5 DIAGNOSTIC CRITERIA FOR MAJOR NEUROCOGNITIVE DISORDER

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

A. evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on both:
   1. concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function;
      and
   2. substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment

B. cognitive deficits interfere with independence in everyday activities (i.e. at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications)
   - **Note**: if deficits do not interfere (as in B) and cognitive impairments are mild-moderate (as in A.2), this is considered "mild neurocognitive disorder"; see Neurology, N21

C. cognitive deficits do not occur exclusively in the context of a delirium

D. cognitive deficits are not better explained by another mental disorder (i.e. major depressive disorder, schizophrenia)

E. in the case of neurodegenerative dementias such as Alzheimer's Disease, disturbances should be of insidious onset and progressive

**The 4 As of Dementia**
**A**mnesia
**A**phasia
**A**praxia
**A**gnosia

**The "Mini Cog" Rapid Assessment**
- 3 word immediate recall
- Clock drawn to "10 past 11"
- 3 word delayed recall

Specify whether due to:

| | | | |
|---|---|---|---|
| Alzheimer's disease | Traumatic brain injury | Prion disease | Multiple etiologies |
| Frontotemporal lobar degeneration | Normal pressure hydrocephalus | Parkinson's disease | Unspecified |
| Lewy body disease | Substance/medication use | Huntington's disease | |
| Vascular disease | HIV infection | Another medical condition | |

## Epidemiology
- prevalence increases with age: 5% in patients >65 yr of age; 35-50% in patients >85 yr of age
- probability of dementia in an older person with reported memory loss is estimated to be 60%
- prevalence is increased in people with Down's syndrome and head trauma
- Alzheimer's disease comprises >50% of cases; vascular causes comprise approximately 15% of cases (other causes of dementia neurocognitive disorder – see Neurology, N21)
- average duration of illness from onset of symptoms to death is 8-10 yr

## Subtypes
- with or without behavioural disturbance (i.e. wandering, agitation)
- early-onset: <65 yr
- late-onset: >65 yr

## Investigations (rule out reversible causes)
- standard "neurocognitive work-up": see *Delirium*, PS22
- as indicated: VDRL, HIV, LP, CXR, EEG, SPECT, head CT, or MRI
- indications for head imaging: same as for delirium, plus: age <60, rapid onset (unexplained decline in cognition or function over 1-2 mo), dementia of relatively short duration (<2 yr), recent significant head trauma, unexplained neurological symptoms (new onset of severe headache/seizures)

## Management
- see Neurology, N21 for further management
- treat underlying medical problems and prevent new ones
- provide orientation cues for patient (i.e. clock, calendar)
- provide education and support for patient and family (i.e. day programs, respite care, support groups, home care)
- consider power of attorney/living will and long-term care plan (nursing home)
- inform Ministry of Transportation about patient's inability to drive safely
- consider pharmacological therapy
  - cholinesterase inhibitors (donepezil [Aricept®], rivastigmine, galantamine) for mild to severe disease
  - NMDA receptor antagonist (memantine) for moderate to severe disease
  - low-dose antipsychotics (i.e. risperidone, aripripazole), escitalopram, or trazodone if behavioural or emotional symptoms prominent – start low and go slow
  - reassess pharmacological therapy every 3 mo

**Flags for Differentiating Most Common Causes of Dementia**

**Alzheimer's disease**: predominantly memory and learning issues
**Frontotemporal degeneration**: language type (early preservation), behavioural type (apathy/disinhibition/self-neglect)
**Lewy body disease**: recurrent, soft visual hallucinations (e.g. rabbits), autonomic impairment (falls, hypotension), EPS, does not respond well to pharmacotherapy, fluctuating degree of cognitive impairment
**Vascular disease**: vascular risk factors, focal neurological signs, abrupt onset, stepwise progression
**Normal pressure hydrocephalus**: abnormal gait, early incontinence, rapidly progressive

**Table 3. Comparison of Dementia, Delirium, and Cognitive Impairment Associated with Depression**

| | Dementia/Major Neurocognitive Disorder | Delirium | Cognitive Impairment Associated with Depression |
|---|---|---|---|
| **Onset** | Gradual/step-wise decline | Acute (hours to days) | Subacute |
| **Duration** | Months-years | Days-weeks | Variable |
| **Natural History** | Progressive<br>Usually irreversible | Fluctuating, reversible High morbidity/ mortality in the elderly | Recurrent<br>Partially reversible |
| **Level of Consciousness** | Normal | Fluctuating (over 24 h) | Normal |
| **Attention** | Not initially affected | Decreased (wandering, easy distraction) | Difficulty concentrating |
| **Orientation** | Intact initially | Impaired (usually to time and place), fluctuates | Intact |
| **Behaviour** | Disinhibition, impairment in ADL/IADL, personality change, loss of social graces | Severe agitation/retardation | Self-harm/suicide |
| **Psychomotor** | Normal | Fluctuates between extremes | Slowing |
| **Sleep Wake Cycle** | Fragmented sleep at night | Reversed sleep wake cycle | Early morning awakening |
| **Mood and Affect** | Labile, anxiety or depression are common in the early stages | Anxious, irritable, fluctuating | Depressed, pervasive |
| **Cognition** | Decreased executive functioning, paucity of thought | Fluctuating | Fluctuating |
| **Memory Loss** | Recent, eventually remote<br>Typically, low insight | Marked recent | Recent<br>More likely to complain |
| **Language** | Agnosia, aphasia, decreased comprehension, repetition, speech (echolalia, palilalia) | Dysnomia, dysgraphia, speech rambling, irrelevant, incoherent, subject changes | Not affected |
| **Delusions** | Compensatory | Nightmarish and poorly formed | Nihilistic, somatic |
| **Hallucinations** | Variable | Visual common | Less common; if present, auditory predominates |
| **Quality of Hallucinations** | Vacuous/bland | Frightening/bizarre | Self-deprecatory |
| **Medical Status** | Variable | Acute illness, drug toxicity | Rule out systemic illness, medications |

# Substance-Related and Addictive Disorders

## Overview

- a neurobiological disorder involving compulsive drug seeking and drug taking, despite adverse consequences, with loss of control over drug use (think issues with the "3 Cs": compulsive, consequences, control)
- dependence is the hallmark of substance use disorders and comes in the following forms:
  - behavioural: substance-seeking activities and pathological use patterns
  - physical: physiologic withdrawal effects without use
  - cognitive: continuous or intermittent cravings for the substance to avoid dysphoria or attain drug state
- abuse: drug use that deviates from the approved social or medical pattern, usually causing impairment or disruption to function in self or others
- these disorders are usually chronic with a relapsing and remitting course
- there are 10 separate classes of substances identified in the DSM-5: alcohol; caffeine; cannabis hallucinogens (phenylcyclidine [or similarly acting arylcyclohexlamines] and other hallucinogens); inhalants; opioids; sedatives, hypnotics, and anxiolytics; stimulants (amphetamine-type substances, cocaine, and other stimulants); tobacco; and other (or unknown) substances

## Epidemiology

- 47% of those with substance abuse have mental health problems
- 29% of those with a mental health disorder have a substance use disorder
- 47% of those with schizophrenia and 25% of those with an anxiety disorder have a substance use disorder

## Etiology

- almost all drugs (and activities) of abuse increase dopamine in the nucleus accumbens, an action that contributes to their euphoric properties and, with repeated use, to their ability to change signaling pathways in the brain's reward system
- substance use disorders arise from multifactorial interactions between genes (personality, neurobiology) and environment (low socioeconomic status, substance-using peers, abuse history, chronic stress)

## Diagnosis

- substance use disorders are measured on a continuum from mild to severe based on the number of criteria met within 12 mo
  - mild: 2-3
  - moderate: 4-5
  - severe: 6 or more
- each specific substance is addressed as a separate use disorder and diagnosed utilizing the same overarching criteria (i.e. a single patient may have moderate alcohol use disorder, and a mild stimulant use disorder)
- testing for illicit drugs is most commonly done on urine or blood samples
  - serum toxicology screen is needed to assess alcohol level
  - toxicology may be helpful in differentiating withdrawal from other mental disorders
- criteria for substance use disorders (**PEC WITH MCAT**)
  - use despite **P**hysical or psychological problem (i.e. alcoholic liver disease or cocaine related nasal problems)
  - failures to fulfill **E**xternal roles at work/school/home
  - **C**raving or a strong desire to use substance
  - **W**ithdrawal
  - continued use despite **I**nterpersonal problems
  - **T**olerance, needing to use more substance to get same effect
  - use in physically **H**azardous situations
  - **M**ore substance used or for longer period than intended
  - unsuccessful attempts to **C**ut down
  - **A**ctivities given up due to substance
  - excessive **T**ime spent on using or finding substance

**Table 4. Substance Symptomatology**

| | Drugs | Symptoms of Intoxication | Symptoms of Withdrawal |
|---|---|---|---|
| **Depressants** | Alcohol, opioids, barbiturates, benzodiazepines, GHB | Euphoria, slurred speech, disinhibition, confusion, poor coordination, coma (severe) | Anxiety, anhedonia, tremor, seizures, insomnia, psychosis, delirium, death |
| **Stimulants** | Amphetamines, methylphenidate, MDMA, cocaine | Euphoria, mania, psychomotor agitation, anxiety, psychosis (especially paranoia), insomnia, cardiovascular complications (stroke, MI, arrhythmias), seizure | 'Crash', craving, dysphoria, suicidality |
| **Hallucinogens** | LSD, mescaline, psilocybin, PCP, ketamine, ibogaine, salvia | Distortion of sensory stimuli and enhancement of feelings, psychosis (++ visual hallucinations), delirium, anxiety (panic), poor coordination | Usually absent |

### General Approach to Assessment

- ask about more socially accepted substances (i.e. nicotine, alcohol) before asking about use of marijuana, misuse of prescription medicines, and about illicit drugs
- obtaining history from family members may be helpful

### General Approach to Treatment

- approach must be appropriate to the patient's current state of change (see Public Health and Preventive Medicine, *Health Promotion Strategies*, PH6)
- patients will only change when the pain of change appears less than the pain of staying the same
- provider can help by providing psychoeducation (emphasize neurobiologic model of addiction), motivation, and hope
- principles of motivational interviewing (see *Psychotherapy*, PS40)
  - non-judgmental stance
  - space for patient to talk and reflect
  - offer accurate empathic reflections back to patient to help frame issue
- encourage and offer referral to evidence based services
  - social: 12-step programs (alcoholics anonymous, narcotics anonymous), family education, and support
  - psychological therapy: addiction counselling, MET, CBT, contingency management, group therapy, family therapy, marital counselling
  - medical management (differs depending on substance): acute detoxification, pharmacologic agents to aid maintenance
- harm reduction whenever possible: safe-sex practices, avoid driving while intoxicated, avoid substances with child care, safe needle practices/exchange, pill-testing kits, reducing tobacco use
- comorbid psychiatric conditions: many will resolve with successful treatment of the substance use disorder but patients who meet full criteria for another disorder should be treated for that disorder with psychological and pharmacologic therapies

**Questions to Characterize Substance Use and Risk Assessment**

- When was the last time you used?
- How long can you go without using?
- By what route (oral ingestion, inhalation (snorting), smoking, IV) do you usually use?
- Are there any triggers that you know will cause you to use?
- How has your substance use affected your work, school, relationships?
- Substances can be very expensive, how do you support your drug use?
- Have you experienced medical or legal consequences of your use?
- Any previous attempts to cut down or quit, and did you experience any withdrawal symptoms?

## Nicotine

- see Family Medicine, FM11

## Alcohol

- see Family Medicine, FM12 and Emergency Medicine, ER54

### History

- Validated screening questionnaire for alcohol use disorders
  - **C** ever felt the need to **C**ut down on your drinking?
  - **A** ever felt **A**nnoyed at criticism of your drinking?
  - **G** ever feel **G**uilty about your drinking?
  - **E** ever need a drink first thing in morning (**E**ye opener)?
  - for men, a score of ≥2 is a positive screen; for women, a score of ≥1 is a positive screen
  - if positive CAGE, then assess further to distinguish between problem drinking and alcohol use disorder

**Confabulations**: the fabrication of imaginary experiences to compensate for memory loss

Make sure to ask about other alcohols: mouthwash, rubbing alcohol, methanol, ethylene glycol, aftershave (may be used as a cheaper alternative)

#### Canada's Low-Risk Alcohol Drinking Guidelines

| Moderate Drinking | | |
|---|---|---|
| Men: 3 or less/d (≤15/wk) | Women: 2 or less/d (≤10/wk) | Elderly: 1 or less/d |

**A "Standard Drink"**
Spirit (40%): 1.5 oz. or 43 mL
Table Wine (12%): 5 oz. or 142 mL
Fortified Wine (18%): 3 oz. or 85 mL
Regular Beer (5%): 12 oz. or 341 mL
OR
1 pint of beer = 1.5 SD
1 bottle of wine = 5 SD
1 "mickey" = 8 SD (375 mL)
"26-er" = 17 SD (750 mL)
"40 oz." = 27 SD

### Alcohol Intoxication

- legal limit for impaired driving is 17 mmol/L (50 mg/dL) reached by 2-3 drinks/h for men and 1-2 drinks/h for women
- coma can occur with >60 mmol/L (non-tolerant drinkers) and 90-120 mmol/L (tolerant drinkers)

### Alcohol Withdrawal

- medical emergency: occurs within 12-48 h after prolonged heavy drinking and can be life-threatening
- ~50% of middle-class, functional individuals with EtOH use disorder have experienced alcohol withdrawal, 80% in hospitalized/homeless individuals
  - alcohol withdrawal can be described as having 4 stages, however not all stages may be experienced:
  - stage 1 (onset 4-12 h after last drink): "the shakes" tremor, sweating, agitation, anorexia, cramps, diarrhea, sleep disturbance, anxiety, insomnia, headache
  - stage 2 (onset 12-24 h): alcoholic hallucinosis: visual, auditory, olfactory or tactile hallucinations
  - stage 3 (onset 24-48 h): alcohol withdrawal seizures, usually tonic-clonic, non-focal, and brief
  - stage 4 (onset 48-72 h): delirium tremens, confusion, delusions, hallucinations, agitation, tremors, autonomic hyperactivity (fever, tachycardia, HTN)
- course: almost completely reversible in young; elderly often left with cognitive deficits
- mortality rate 20% if untreated

**Delirium Tremens (alcohol withdrawal delirium)**

- Autonomic hyperactivity (diaphoresis, tachycardia, increased respiration)
- Hand tremor
- Insomnia
- Psychomotor agitation
- Anxiety
- Nausea or vomiting
- Tonic-clonic seizures
- Visual/tactile/auditory hallucinations
- Persecutory delusions

## Management of Alcohol Withdrawal

- monitor using the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A) scoring system
  - areas of assessment include:
    - physical (5): nausea and vomiting, tremor, agitation, paroxysmal sweats, headache/fullness in head
    - psychological/cognitive (2): anxiety, orientation/clouding of sensorium
    - perceptual (3): tactile disturbances, auditory disturbances, visual disturbances
    - all categories are scored from 0-7 (except: orientation/sensorium 0-4), maximum score of 67 mild <10, moderate 10-20, severe >20

**Table 5. CIWA-A Scale Treatment Protocol for Alcohol Withdrawal**

| | |
|---|---|
| **Basic Protocol** | Diazepam 20 mg PO q1-2h prn until CIWA-A <10 points |
| | Observe 1-2 h after last dose and re-assess on CIWA-A scale |
| | Thiamine 100 mg IM then 100 mg PO OD for 3 d |
| | Supportive care (hydration and nutrition) |
| **History of Withdrawal Seizures** | Diazepam 20 mg PO q1h for minimum of three doses regardless of subsequent CIWA scores |
| **If age >65 or patient has severe liver disease, severe asthma or respiratory failure** | Use a short acting benzodiazepine<br>Lorazepam PO/SL/IM 1-4 mg q1-2h |
| **If Hallucinations are present** | Haloperidol 2-5 mg IM/PO q1-4h – max 5 doses/d or atypical antipsychotics (olanzapine, risperidone) |
| | Diazepam 20 mg x 3 doses as seizure prophylaxis (haloperidol lowers seizure threshold) |
| **Admit to Hospital if** | Still in withdrawal after >80 mg of diazepam |
| | Delirium tremens, recurrent arrhythmias, or multiple seizures |
| | Medically ill or unsafe to discharge home |

## Wernicke-Korsakoff Syndrome

- alcohol-induced amnestic disorders due to thiamine deficiency (poor nutrition or malabsorption)
- necrotic lesions: mammillary bodies, thalamus, brainstem
- Wernicke's encephalopathy (acute and reversible): triad of oculomotor dysfunction such as nystagmus (CN VI palsy), gait ataxia, and confusion
- Korsakoff's syndrome (chronic and only 20% reversible with treatment): anterograde amnesia and confabulation; cannot occur during an acute delirium or dementia and must persist beyond usual duration of intoxication/withdrawal
- management
  - Wernicke's preventative treatment (any patient in withdrawal): thiamine 100-250mg IM/IV x 1 dose
  - Wernicke's acute treatment: thiamine 500 mg IV BID/TID x 72,h then reassess
  - Korsakoff's: IV treatment as for Wernicke's followed by thiamine 100 mg PO TID x 3-12 mo

## Treatment of Alcohol Use Disorder

- non-pharmacological
  - see *General Approach to Treatment*
- pharmacological
  - naltrexone (Revia®): opioid antagonist, shown to be successful in reducing the "high" associated with alcohol, moderately effective in reducing cravings, frequency or intensity of alcohol binges; can be started if still consuming alcohol or abstinent
  - acamprosate (Campral®): NMDA glutamate receptor antagonist; useful in maintaining abstinence and decreasing cravings
  - disulfiram (Antabuse®): prevents oxidation of alcohol (blocks acetaldehyde dehydrogenase); with alcohol consumption, acetaldehyde accumulates to cause a toxic reaction (vomiting, tachycardia, death); if patient relapses, must wait 48 h before restarting Antabuse®; prescribed only when treatment goal is abstinence; RCT evidence is generally poor or negative
  - some evidence for the use of gabapentin, topiramate and ondansetron as anti-craving agents, but not Health Canada approved for this indication

# Opioids

- types of opioids: heroin, morphine, oxycodone, Tylenol #3® (codeine), hydromorphone, fentanyl
- major risks associated with the use of contaminated needles: increased risk of hepatitis B and C, bacterial endocarditis, and HIV/AIDS
- recent considerations of inadvertent overdose secondary to contamination with fentanyl in the drug supply "opioid crisis" leading to 9000 deaths in Canada between January 2016 and June 2018

## Acute Intoxication

- direct effect on receptors in CNS resulting in decreased pain perception, sedation, decreased sex drive, nausea/vomiting, decreased GI motility (constipation and anorexia), and respiratory depression

## Toxic Reaction

- medical emergency: typical syndrome includes shallow respirations, miosis, bradycardia, hypothermia, decreased level of consciousness
- management
  - ABCs
  - IV glucose
  - naloxone hydrochloride (Narcan®): 0.4 mg up to 2 mg IV for diagnosis
  - treatment: intubation and mechanical ventilation, ± naloxone drip, until patient alert without naloxone (up to >48 h with long-acting opioids)
- caution: opioids have a longer half-life than naloxone; may need to observe for toxic reaction for at least 24 h

## Withdrawal

- symptoms: dysphoric mood, insomnia, drug-craving, myalgias, nausea or vomiting, yawning, chills, lacrimation, rhinorrhea, pupillary dilation, piloerection, sweating, diarrhea, fever
- onset: 6-12 h (depending on half-life of opioid used); duration: 5-10 d
- complications: loss of tolerance (overdose on relapse), miscarriage, premature labour
- management: long-acting oral opioids (methadone, buprenorphine), α-adrenergic agonists (clonidine)

## Treatment of Opioid Use Disorder

- see *General Approach to Treatment*, PS26
- long-term treatment may include maintenance treatment with methadone (opioid agonist) or buprenorphine (mixed agonist-antagonist)
- Suboxone® formulation includes naloxone in addition to buprenorphine, in an effort to prevent injection of the drug. When naloxone is injected, it will precipitate opiate withdrawal and block the opiate effect of buprenorphine; however, it will not have this antagonist action when taken sublingually
- decreasing risk of overdose: patients with opiate use disorder should be encouraged to carry a naloxone kit and educated on ways to limit overdose risk (i.e. use with a friend, avoid mixing drugs)

**Opioid Antagonists**
**Naltrexone vs. Naloxone**

Naltrexone (Revia®)
- Can be used for EtOH dependence (although not routinely used)
- Long half life (h)

Naloxone (Narcan®)
- Used for life-threatening CNS/respiratory depression in opioid overdose
- Short half life (<1 h)
- Very fast acting (min)
- High affinity for opioid receptor
- Induces opioid withdrawal symptoms

**Maintenance Medication for Opiate Addiction: The Foundation of Recovery**
*J Addict Dis* 2012;31:207-225
Maintenance treatment of opioid addiction with methadone or buprenorphine is associated with retention in treatment, reduction in illicit opiate use, decreased craving, and improved social function. Recently, studies showing extended release naltrexone injections have showed some promise.

# Cocaine

- street names: blow, C, coke, crack, flake, freebase, rock, snow
- alkaloid extracted from leaves of the coca plant; blocks presynaptic uptake of serotonin (causing euphoria), dopamine (linked to its addictive effect), norepinephrine and epinephrine (causing vasospasm, HTN)
- sodium channel blockade: cocaine slows or blocks nerve conduction and acts as a local anesthetic by altering recovery of neuronal $Na^+$ channels; it has a similar effect on cardiac $Na^+$ channels and in overdose can manifest on ECG as prolongation of the QRS complex
- self-administered by inhalation (90% bioavailability), insufflation (i.e. intranasal; 80% bioavailability), or intravenous route
- onset and duration of action: onset within seconds if inhaled, lasting 15-30 min; onset in 3-5 min if insufflated, blood levels peak at 10-20 min with effects beginning to fade after 45-60 min; cocaine has a biologic half-life of 1 h, thus repeated self-administration is common among users to maintain an effect

## Intoxication

- elation, euphoria, pressured speech, restlessness, sympathetic stimulation (i.e. tachycardia, mydriasis, sweating, pupillary dilatation, hypertension)
- prolonged use may result in paranoia and psychosis

## Overdose

- medical emergency: HTN, tachycardia, tonic-clonic seizures, dyspnea, and ventricular arrhythmias
- treatment with IV diazepam to control seizures
- beta-blockers (incl. labetalol or propranolol) are not recommended because of risk from unopposed alpha-adrenergic stimulation

## Withdrawal

- initial "crash" (1-48 h): increased sleep, increased appetite, dysphoria
- withdrawal (1-10 wk): dysphoric mood plus fatigue, irritability, vivid unpleasant dreams, insomnia or hypersomnia, psychomotor agitation or retardation
- complications: relapse, suicide (significant increase in suicide during withdrawal period)
- management: supportive management

**Common Presentations of Drug Use**

| System | Findings |
|---|---|
| **General** | Weight loss (especially cocaine, heroin)<br>Injected conjunctiva (cannabis)<br>Pinpoint pupils (opioids)<br>Track marks (injection drugs) |
| **MSK** | Trauma |
| **GI** | Viral hepatitis (injection drugs)<br>Unexplained elevations in ALT (injection drugs) |
| **Behavioural** | Missed appointments<br>Non-compliance<br>Drug-seeking (especially benzodiazepines, opioids) |
| **Psychological** | Insomnia<br>Fatigue<br>Depression<br>Flat affect (benzodiazepines, barbiturates)<br>Paranoia (cocaine)<br>Psychosis (cocaine, cannabis, hallucinogens) |
| **Social** | Marital discord<br>Family violence<br>Work/school<br>Absenteeism and poor performance |

### Treatment of Cocaine Use Disorder
- see *General Approach to Treatment*, PS26
- no pharmacologic agents have widespread evidence or acceptance of use

### Complications
- cardiovascular: arrhythmias, MI, CVA, ruptured AAA, chest pain (accounts for 40% of all cocaine-related ED visits)
- neurologic: seizures
- psychiatric: psychosis, delirium, suicidal ideation
- other: nasal septal deterioration, acute/chronic lung injury "crack lung", possible increased risk of connective tissue disease

## Amphetamines

- includes prescription medications for ADHD such as Ritalin® and Adderall® and street drugs such as crystal meth
- intoxication characterized by euphoria, improved concentration, sympathetic and behavioural hyperactivity, and at high doses. can mimic symptoms of psychosis or mania; can eventually cause coma
- chronic use can produce psychosis which can resemble schizophrenia with agitation, paranoia, delusions. and hallucinations
- withdrawal symptoms include dysphoria, fatigue, and restlessness
- treatment of amphetamine induced psychosis: antipsychotics for acute presentation, benzodiazepines for agitation, β-blockers for tachycardia, hypertension

## Cannabis

- cannabis (marijuana) is the most commonly used recreational drug
- psychoactive substance: delta-9-tetrahydrocannabinol (Δ9-THC)
- general clinical manifestations: intoxication characterized by tachycardia, conjunctival vascular engorgement, dry mouth, altered sensorium, increased appetite, and muscle relaxation
- neuropsychiatric effects:
  - altered mood, perception, and thought content: increased sense of well-being, euphoria/laughter
  - impaired cognitive and psychomotor performance: reduced reaction time, impaired attention, concentration, and short-term memory. It may also impair motor coordination required to complete complex tasks requiring divided attention. Notably, psychomotor impairments may interfere with one's ability to operate heavy machinery such as automobiles
- inhaled marijuana: onset of psychoactive effects occurs rapidly with peak effects felt 15-30 min after intake and lasting up to 4 h
  - acute exacerbation in patients with asthma may be a complication with inhalation
- ingested marijuana: following oral ingestion, psychotrophic effects set in with a delay of 30-90 min, reach their maximum after 2-3 h and last for about 4-12 h depending on dose
- high doses can cause depersonalization, paranoia, anxiety and may trigger psychosis and schizophrenia if predisposed
- chronic use is associated with tolerance and an apathetic, amotivational state
- assessment: standard urine drug screens
- treatment of cannabis use disorder: see General Approach to Treatment, PS23
- cessation following heavy use produces a significant withdrawal syndrome: irritability, anxiety, insomnia, decreased food intake

## Hallucinogens

- types of hallucinogens by primary action
  - 5-HT2A agonists: LSD, mescaline (peyote), psilocybin mushrooms, DMT (ayahuasca)
  - NMDA antagonists: PCP, ketamine
  - κ-opioid agonists: salvia divinorum, ibogaine
- 5-HT2A agonists are most commonly used; intoxication characterized by tachycardia, HTN, mydriasis, tremor, hyperpyrexia, and a variety of perceptual, mood and cognitive changes (rarely, if ever, deadly; treat vitals symptomatically)
- psychological effects of high doses: depersonalization, derealization, paranoia, and anxiety (panic with agoraphobia)
- tolerance develops rapidly (hours-days) to most hallucinogens so physical dependency is virtually impossible, although psychological dependency and problematic usage patterns can still occur
- no specific withdrawal syndrome characterized
- management of acute intoxication: support, reassurance, diminished stimulation; benzodiazepines or high potency antipsychotics seldom required (if used, use small doses), minimize use of restraints
- long term adverse effects: controversial role in triggering psychiatric disorders, particularly mood or psychosis, thought to be chiefly in individuals with genetic or other risk factors
- Hallucinogen Persisting Perception Disorder: DSM-5 diagnosis characterized by long lasting, spontaneous, intermittent recurrences of visual perceptual changes reminiscent of those experienced with hallucinogen exposure



**Cannabinoid Hyperemesis Syndrome**
An interesting and relatively new clinical phenomenon associated with chronic cannabis use characterized by cyclical, recurrent severe nausea, vomiting, and colicky pain. Possibly due to increased potency of available THC products. Patients often present to ED in acute distress with no evidence of specific GI pathology. Many patients will successfully self-medicate with hot baths or showers



**Medical Uses of Marijuana**
- Anorexia-cachexia (AIDS, cancer)
- Spasticity, muscle spasms (multiple sclerosis, spinal cord injury)
- Levodopa-induced dyskinesia (Parkinson's Disease)
- Controlling tics and obsessive-compulsive behaviour (Tourette's syndrome)
- Reducing intra-ocular pressure (glaucoma)



**Cannabis Use and Risk of Psychotic or Affective Mental Health Outcomes: A Systematic Review**
The Lancet 2007;370:319-328
**Purpose**: To review the evidence for cannabis use and occurrence of psychotic or affective mental health outcomes.
**Study Characteristics**: A meta-analysis of 35 population-based longitudinal studies, or case-control studies nested within longitudinal designs.
**Results**: There was an increased risk of any psychotic outcome in individuals who had ever used cannabis (pooled adjusted odds ratio =1.41, 95% CI 1.20-1.65). Findings were consistent with a dose-response effect, with greater risk in people who used cannabis more frequently (2.09, 95% CI, 1.54-2.84). Findings for depression, suicidal thoughts, and anxiety outcomes were less consistent. In both cases (psychotic and affective outcomes), a substantial confounding effect was present.
**Conclusions**: The findings are consistent with the view that cannabis increases risk of psychotic outcomes independent of transient intoxication effects, although evidence is less strong for affective outcomes. Although cannabis use and the development of psychosis are strongly associated, it is difficult to determine causality and it is possible that the association results from confounding factors or bias. The authors did conclude that there is sufficient evidence to warn young people that using cannabis could increase their risk of developing a psychotic illness later in life.

# "Club Drugs"

**Table 6. The Mechanism and Effects of Common "Club Drugs"**

| Drug | Mechanism | Effect | Adverse Effects |
|---|---|---|---|
| **MDMA ("Ecstasy", "X", "E", "M", "Molly")** | Acts on serotonergic and dopaminergic pathways, properties of a hallucinogen and stimulant | Enhanced sensorium; feelings of well-being, empathy | Diaphoresis, tachycardia, fatigue, muscle spasms (especially jaw clenching), ataxia, hyperthermia, arrhythmias, DIC, rhabdomyolysis, renal failure, seizures, death |
| **Gamma Hydroxybutyrate (GHB, "G", "Liquid Ecstasy")** | Biphasic dopamine response (inhibition then release) and releases opiate-like substance | Euphoric effects, increased aggression, impaired judgment | Diaphoresis, tachycardia, fatigue, muscle spasms (especially jaw clenching), ataxia, severe withdrawal from abrupt cessation of high doses: tremor, seizures, psychosis |
| **Flunitrazepam (Rohypnol®, "Roofies", "Rope", "The Forget Pill")** | Potent benzodiazepine, rapid oral absorption | Sedation, psychomotor impairment, amnestic effects, decreased sexual inhibition | CNS depression with EtOH |
| **Ketamine ("Special K", "Kit-Kat")** | NMDA receptor antagonist, rapid-acting general anesthetic used in pediatrics and by veterinarians | "Dissociative" state, profound amnesia/ analgesia, hallucinations and sympathomimetic effects | Psychological distress, accidents due to intensity of experience and lack of bodily control<br>In overdose: decreased LOC, respiratory depression, catatonia |
| **Methamphetamine ("speed", "meth", "chalk", "ice", "crystal")** | Amphetamine stimulant, induces norepinephrine, dopamine, and serotonin release | Rush begins in min, effects last 6-8 h, increased activity, decreased appetite, general sense of well-being, tolerance occurs quickly, users often binge and crash | Short-term use: high agitation, rage, violent behaviour, occasionally hyperthermia and convulsions<br>Long-term use: addiction, anxiety, confusion, insomnia, paranoia, auditory and tactile hallucinations (especially formication), delusions, mood disturbance, suicidal and homicidal thoughts, stroke<br>May be contaminated with lead, and IV users may present with acute lead poisoning |
| **Phencyclidine ("PCP", "angel dust")** | Not understood, used by veterinarians to immobilize large animals | Amnestic, euphoric, hallucinatory state | Horizontal/vertical nystagmus, myoclonus, ataxia, autonomic instability (treat with diazepam IV), prolonged agitated psychosis (treat with haloperidol); high risk for suicide; violence towards others<br>High dose can cause coma |



**Date Rape Drugs**
- GHB
- Flunitrazepam (Rohypnol®)
- Ketamine



**Formication**
Tactile hallucination that insects or snakes are crawling over or under the skin (especially associated with crystal meth use)



**Emerging Medical Uses of Hallucinogens**
Many hallucinogens are currently under investigation for therapeutic benefit; LSD & Psilocybin for end of life anxiety, MDMA for PTSD, Ketamine for rapid treatment of depression, ibogaine derivatives for addiction

# Somatic Symptom and Related Disorders

## General Characteristics

- physical signs and symptoms lacking objective medical support in the presence of psychological factors that are judged to be important in the initiation, exacerbation, or maintenance of the disturbance
- cause significant distress or impairment in functioning
- symptoms are produced unconsciously and are not the result of malingering or factitious disorder, which are disorders of voluntary presentation of symptoms (or intentionally inducing, i.e. injecting feces) for secondary gain
- primary gain: somatic symptom represents a symbolic resolution of an unconscious psychological conflict; serves to reduce anxiety and conflict with no external incentive
- secondary gain: the sick role; external benefits obtained or unpleasant duties avoided (i.e. work)

## Management of Somatic Symptom and Related Disorders

- brief, regular scheduled visits with GP to facilitate therapeutic relationship and help patient feel supported
- good, clear communication among all involved care providers
- limit number of physicians involved in care, minimize medical investigations, coordinate necessary investigations
- emphasis on what the patient can change and control; the psychosocial coping skills, not their physical symptoms (functional recovery > explanation of symptoms)
- focus on functional improvement (physiotherapy, occupational therapy), provide psychoeducation to validate suffering in the face of medically unexplained symptoms
- psychotherapy: CBT, mindfulness interventions, biofeedback
- minimize psychotropic drugs: anxiolytics in short-term only, antidepressants for comorbid depression and anxiety



**Malingering**: intentional production of false or grossly exaggerated physical or psychological symptoms, motivated by secondary gain/external reward (i.e. avoiding work, obtaining financial compensation, or obtaining drugs)

**Factitious Disorder**: intentional production or feigning of physical or psychological signs or symptoms. Unlike malingering patients are not motivated by secondary gain but rather may seek sympathy, nurturance, and attention

# Somatic Symptom Disorder

### DSM-5 DIAGNOSTIC CRITERIA FOR SOMATIC SYMPTOM DISORDER

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A. one or more somatic symptoms that are distressing or result in significant disruption of daily life
B. excessive thoughts, feelings, or behaviours related to the somatic symptoms or associated health concerns as manifested by at least one of the following:
   1. disproportionate and persistent thoughts about the seriousness of one's symptoms
   2. persistently high level of anxiety about health or symptoms
   3. excessive time and energy devoted to these symptoms or health concerns
C. although any one somatic symptom may not be continuously present, the state of being symptomatic is persistent (typically >6 mo)

- **somatic symptom disorder with predominant pain** (previously pain disorder) for those whose somatic symptom is primarily pain
- patients have physical symptoms and believe these symptoms represent the manifestation of a serious illness
- persistent belief despite negative medical investigations and may develop different symptoms over time
- lifetime prevalence may be around 5-7% in the general adult population
- females tend to report more somatic symptoms than males do, cultural factors may influence sex ratio
- complications: anxiety and depression commonly comorbid (up to 80%), unnecessary medications, or surgery
- often a misdiagnosis for an insidious illness so rule out all organic illnesses (i.e. multiple sclerosis)

# Illness Anxiety Disorder

- preoccupation with fear of having, or the idea that one has, a serious disease, to the point of causing significant impairment
- convictions persist despite negative investigations and medical reassurance
- somatic symptoms are mild or not present
- there is a high level of anxiety about health and the individual is easily alarmed about personal health status
- person engages in maladaptive behaviour such as excessive physical checking or total healthcare avoidance
- duration is ≥6 mo; onset in 3rd-4th decade of life
- a new diagnostic entity so epidemiology is not well known; however, it is likely less common than somatic symptom disorder
- possible role for SSRIs due to generally high level of anxiety
- specifiers: care-seeking type or care-avoidant type

# Conversion Disorder (Functional Neurological Symptom Disorder)

- ≥1 symptoms or deficits affecting voluntary motor or sensory function that mimic a neurological or GMC (i.e. impaired coordination, local paralysis, double vision, seizures, or convulsions)
- does not need to be preceded by a psychological event as per previous DSM criteria, however this is still worth exploring as many patients will present after such an event or related to a medical diagnosis in a first-degree relative
- 2-5/100,000 in general population; 5% of referrals to neurology clinics
- more common in rural populations and in individuals with little medical knowledge
- spontaneous remission in 95% of acute cases, 50% of chronic cases (>6 mo)
- incompatible findings detected from specific neurological testing can help differentiate between functional and neurological origin (i.e. Hoover's sign and dermatome testing)
- specifiers: acute episode (<6 mo symptom duration), chronic episode (>6 mo symptom duration), with psychological stressor, without psychological stressor



**La belle indifference**: an inappropriately cavalier patient attitude in the face of serious symptoms; classically associated with conversion disorder

**Table 7. Differential of Somatic Symptom and Related Disorders**

| | Somatic Symptom Disorder | Illness Anxiety Disorder | Conversion Disorder | Factitious Disorder | Malingering |
|---|---|---|---|---|---|
| **Somatic Symptoms** | Present | Mild or absent | Neurologic, voluntary motor or sensory | Psychological or physical | Psychological or physical |
| **Symptoms Produced** | Unconsciously | Unconsciously | Unconsciously | Consciously | Consciously |
| **Physical Findings** | Absent | Absent | Incompatible | Possible, attempts to falsify | Possible, attempts to falsify |

# Dissociative Disorders

### Definition
- severe dissociation resulting in breakdown of integrated functions of consciousness and perception of self
- differential diagnosis: PTSD, acute stress disorder, borderline personality disorder, somatic symptom disorder, substance abuse, GMC (various neurologic disorders including complex/partial seizures, migraine, Cotard syndrome)

## Dissociative Identity Disorder

- disruption of identity characterized by ≥2 distinct personality states or an experience of possession
- can manifest as sudden alterations in sense of self and agency (ego-dystonic emotions, behaviours, speech)
- features recurrent episodes of amnesia (declarative or procedural)

## Dissociative Amnesia

- inability to recall important autobiographical information, usually of a traumatic or stressful nature, that is inconsistent with normal forgetting and not attributable to a psychiatric disorder or medical illness
- localized/selective amnesia: failure to recall all/some events during a prescribed period of time
- generalized amnesia: (more rare) complete loss of memory for one's life history, ± procedural knowledge, ± semantic knowledge; usually sudden onset; often presents with perplexity, disorientation, and aimless wandering



**Fugue**
Purposeful travel or bewildered wandering while in amnesic state

## Depersonalization/Derealization Disorder

- persistent or recurrent episodes of one or both of:
  - depersonalization: experiences of detachment from oneself, feelings of unreality, or being an outside observer to one's thoughts, feelings, speech, and actions (can feature distortions in perception including time, as well as emotional and physical numbing)
  - derealization: experiences of unreality or detachment with respect to the surroundings (i.e. feeling as if in a dream, or that the world is not real; external visual world is foggy or distorted)
- transient (s-h) experiences of this nature are quite common in the general population
- episodes can range from h-yr, patients are often quite distressed and verbalize concern of "going crazy"



During depersonalization or derealization, patients usually have intact reality testing, which adds to their alarming nature

# Sleep Disorders

- for more information regarding normal sleep cycles and the illnesses described, see Neurology, *Sleep Disorders*, N46

### Overview
- adequate sleep is essential to normal functioning; deprivation can lead to cognitive impairment and increased mortality
- circadian rhythms help regulate mood and cognitive performance
- neurotransmitters commonly implicated in psychiatric illnesses also regulate sleep
  - acetylcholine activity and decreased activity of monoamine neurotransmitters is associated with greater REM sleep
  - decreased adrenergic and cholinergic activity are associated with NREM sleep
- depression is associated with decreased Δ (deep, slow-wave) sleep, decreased REM latency, and increased REM density
- criteria
  - must cause significant distress or impairment in normal functioning
  - not due to a GMC or medications/drugs (unless specified)

### Management
- pharmacological treatments are illness-specific
  - non-benzodiazepines preferable (i.e. trazodone, zoplicone, quetiapine), but benzodiazepines a short term option
  - medication should not be prescribed without having first made a diagnosis and considering major psychiatric illnesses (major depression and alcohol use disorders are common etiologies)
- sleep hygiene is a simple, effective, but often underutilized method for addressing sleep disturbances; recommendations include:
  - waking up and going to bed at same time every day, including on weekends
  - avoiding long periods of wakefulness in bed
  - not using bed for non-sleep activities (reading, TV, work)
  - avoiding screens, especially smartphones and ipads in the hour before bed
  - avoiding napping
  - discontinuing or reducing consumption of alcohol, caffeine, drugs
  - exercising at least 3-4x per week (but not in the evening, if this interferes with sleep)
- Cognitive Behavioural Therapy for insomnia (CBTi)

**Table 8. Major DSM-5 Sleep-Wake Disorders**

Note: For more information regarding specific disorders, see: Neurology, *Sleep Disorders*, N46; Family Medicine, *Sleep Disorders*, FM44; and Respirology, *Sleep Apnea*, R28

| Category | Disorder | Description |
|---|---|---|
| **(Uncategorized)** | **Insomnia disorder** | Difficulty sleeping |
| | **Hypersomnolence disorder** | Feeling sleepy throughout the day |
| | **Narcolepsy** | Recurrent attacks of irrepressible need to sleep |
| | **Circadian rhythm sleep-wake disorders** | Insomnia or excessive sleepiness due to misalignment or alteration in endogenous circadian rhythm |
| | **Restless legs syndrome** | Uncomfortable, frequent urge to move legs at night |
| | **Substance/medication-induced sleep disorder** | Disturbance in sleep (insomnia or daytime sleepiness) caused by substance/medication intoxication or withdrawal |
| **Breathing-Related Sleep Disorders** | **Obstructive sleep apnea hypopnea** | Breathing issues due to obstruction |
| | **Central sleep apnea** | Breathing issues due to aberrant brain signaling |
| | **Sleep-related hypoventilation** | Breathing issues due to decreased responsiveness to carbon dioxide levels |
| **Parasomnias** | **Non-rapid eye movement sleep arousal disorders** | Incomplete awakening from sleep, complex motor behaviour without conscious awareness; amnesia regarding episodes; includes symptoms of: |
| | | **Sleepwalking**: rising from bed and walking about, blank face, unresponsive, awakened with difficulty |
| | | **Sleep terrors**: recurrent episodes of abrupt terror arousals from sleep, usually beginning with a panicky scream, intense fear and autonomic arousal, relative unresponsiveness to comfort during episodes |
| | | **Specifiers**: sleep-related sexual behaviour (sexsomnia) and sleep-related eating |
| | **Nightmare disorder** | Repeated extended, extremely dysphoric, often very vivid, well-remembered dreams that usually involve significant threats; rapid orientation and alertness on awakening with autonomic arousal |
| | **Rapid eye movement sleep behaviour disorder** | Arousal during sleep, associated with vocalization and/or complex motor behaviours; can cause violent injuries; rapid orientation and alertness on awakening |

# Sexuality and Gender

## Gender Dysphoria

### Definition
- the distress that may coincide with conflict between one's experienced/expressed gender and one's assigned gender

### Typical Presentation
- strong and persistent cross-gender identification
- desire to be rid of current primary/secondary sex characteristics and to gain the primary/secondary sex characteristics of their identified gender
- repeated stated desire or insistence that one is of the opposite sex
- preference for cross-dressing, cross-gender roles in make-believe play
- strong desire to participate in the stereotypical games and pastimes of the opposite sex
- strong preference for playmates of the opposite sex
- significant distress or impairment in functioning and persistent discomfort with his or her sex or gender role

### Treatment
- psychotherapy
- hormonal therapy
- gender affirming surgery (old term: sexual reassignment surgery)

## Paraphilic Disorders

### Definition
- intense and persistent sexual arousal that is elicited by something other than genital stimulation or preparatory fondling with phenotypically normal, physically mature, consenting human partners
- paraphilic disorder: paraphilia that causes distress or functional impairment to the individual, or a paraphilia whose realization entails personal harm, or risk of harming others
- subtypes: voyeuristic, exhibitionistic, frotteuristic, sexual masochism, sexual sadism, pedophilic, fetishistic, transvestic, other specified paraphilic disorder, unspecified paraphilic disorder
- rarely self-referred; come to medical attention through interpersonal or legal conflict

- person usually has more than one paraphilia; 5% of paraphilias attributed to women
- typical presentation: begins in childhood or early adolescence; increasing complexity and stability with age
- chronic, decreases with advancing age but may increase with stress

### Treatment
- anti-androgen drugs
- behaviour modification
- psychotherapy

### SEXUAL DYSFUNCTION
- see Gynecology, GY32 and Urology, U33

# Eating Disorders

### Definition
- eating disorders are characterized by a persistent disturbance of eating that impairs psychosocial functioning or health
- disorders include: anorexia nervosa, avoidant/restrictive food intake disorder, binge eating disorder, bulimia nervosa, pica, and rumination disorder

### Epidemiology
- anorexia nervosa (AN): 1% of adolescent and young adult females; onset 13-20 yr old
- bulimia nervosa (BN): 2-4% of adolescent and young adult females; onset 16-18 yr old
- F:M=10:1; mortality 5-10%

### Etiology
- multifactorial: psychological, sociological, and biological associations
- individual: perfectionism, lack of control in other life areas, history of sexual abuse
- personality: obsessive-compulsive, histrionic, borderline
- familial: maintenance of weight equilibrium and control in dysfunctional family
- cultural factors: prevalent in industrialized societies, idealization of thinness in the media
- genetic factors
  - AN: 6% prevalence in siblings, with one study of twin pairs finding concordance in 9 of 12 monozygotic pairs versus concordance in 1 of 14 dizygotic pairs
  - BN: higher familial incidence of affective disorders than the general population

### Risk Factors
- physical factors: obesity, chronic medical illness (i.e. DM)
- psychological factors: individuals who by career choice are expected to be thin, family history (mood disorders, eating disorders, substance abuse), history of sexual abuse (especially for BN), homosexual males, competitive athletes, concurrent associated mental illness (depression, OCD, anxiety disorder [especially panic and agoraphobia], substance abuse [specifically for BN])

**Eating Disorder Screening**
Method to identify patients with eating disorders. A "Yes" to two or more questions is associated with a sensitivity and specificity of 78 and 88 percent, respectively

**SCOFF**
- Do you make yourself **S**ick because you feel uncomfortably full?
- Do you worry you have lost **C**ontrol over how much you eat?
- Have you recently lost more than **O**ne stone (14 pounds or 6.35 kg) in a 3 mo period?
- Do you believe yourself to be **F**at when others say you are too thin?
- Would you say that **F**ood dominates your life?

# Anorexia Nervosa

### DSM-5 DIAGNOSTIC CRITERIA FOR ANOREXIA NERVOSA
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A. intake and weight: restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health; significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected
B. fear or behaviour: intense fear of gaining weight or of becoming fat, or persistent behaviour that interferes with weight gain, even though at a significantly low weight
C. perception: disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight
- **specifiers**: partial remission, full remission, severity based on BMI (mild = BMI >17 kg/m$^2$, moderate = BMI 16-16.99 kg/m$^2$, severe = BMI 15-15.99 kg/m$^2$, extreme = BMI <15 kg/m$^2$), type (restricting = during last 3 mo no episodes of binge-eating or purging vs. binge-eating/purging type = in last 3 mo have participated in recurrent episodes of binge-eating/purging)

**Athletic Triad**
- Disordered eating
- Amenorrhea
- Osteoporosis

Some patients with insulin-dependent DM may stop their insulin in order to lose weight

### Management
- psychotherapy: individual, group, family: address food and body perception, coping mechanisms, health effects
- medications of little value
- outpatient and inpatient programs are available
- inpatient hospitalization for treatment of eating disorders is rarely on an acute basis (unless there is a concurrent psychiatric reason for emergent admission i.e. suicide risk)
- criteria to admit to medical ward for hospitalization: <65% of standard body weight (<85% of standard body weight for adolescents), hypovolemia requiring intravenous fluid, heart rate <40 bpm, abnormal serum chemistry, or if actively suicidal
- agree on target body weight on admission and reassure this weight will not be surpassed

- monitor for complications of AN (see Table 9)
- monitor for refeeding syndrome
  - potentially life-threatening metabolic response to refeeding in severely malnourished patients resulting in severe shifts in fluid and electrolyte levels
  - complications include hypophosphatemia, congestive heart failure, cardiac arrhythmias, delirium, and death
  - prevention: slow refeeding, gradual increase in nutrition, supplemental phosphorus, and close monitoring of electrolytes and cardiac status

### Prognosis
- early intervention much more effective (adolescent onset has much better prognosis than adult onset)
- 1 in 10 adolescents continue to have AN as adults
- with treatment, 70% resume a weight of at least 85% of expected levels and about 50% resume normal menstrual function
- eating peculiarities and associated psychiatric symptoms are common and persistent
- long-term mortality: 10-20% of patients hospitalized will die in next 10-30 yr (secondary to severe and chronic starvation, metabolic or cardiac catastrophes, with a significant proportion committing suicide)

## Bulimia Nervosa

### DSM-5 DIAGNOSTIC CRITERIA FOR BULIMIA NERVOSA

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A. recurrent episodes of binge-eating; an episode of binge-eating is characterized by both of the following
  - eating, in a discrete period of time, an amount of food that is definitely larger than what most individuals would eat during a similar period of time and under similar circumstances
  - a sense of lack of control over eating during the episode

B. recurrent inappropriate compensatory behaviour in order to prevent weight gain, such as self-induced vomiting, misuse of laxatives, diuretics, enemas, or other medications, fasting, or excessive exercise

C. the binge-eating and inappropriate compensatory behaviours both occur, on average, at least once a week for 3 mo

D. self-evaluation is unduly influenced by body shape and weight

E. the disturbance does not occur exclusively during episodes of AN

- **specifiers**: partial remission, full remission, severity (measured in # of inappropriate compensatory behaviours/wk: mild = 1-3, moderate = 4-7, severe = 8-13, extreme = 14+)

### Associated Features
- fatigue and muscle weakness due to repetitive vomiting and fluid/electrolyte imbalance
- tooth decay
- swollen appearance around angle of jaw and puffiness of eye sockets due to fluid retention
- reddened knuckles, Russell's sign (knuckle callus from self-induced vomiting)
- trouble concentrating
- weight fluctuation over time

### Management
- admission for significant electrolyte abnormalities
- biological: treatment of starvation effects, SSRIs (fluoxetine most evidence) as adjunct
- psychological: develop trusting relationship with therapist to explore personal etiology and triggers, CBT, family therapy, recognition of health risks
- social: challenge destructive societal views of women, use of hospital environment to provide external patterning for normative eating behaviour

### Prognosis
- relapsing/remitting disease
- good prognostic factors: onset before age 15, achieving a healthy weight within 2 yr of treatment
- poor prognostic factors: later age of onset, previous hospitalizations, individual and familial disturbance
- 60% good treatment outcome, 30% intermediate outcome, 10% poor outcome

## Binge-Eating Disorder

### Definition
- recurrent episodes of binge-eating (as defined by criteria A of BN) that are associated with eating much more rapidly than normal, eating until feeling uncomfortably full, eating large amounts when not physically hungry, eating alone because embarrassed by how much one is eating, feeling disgusted with self/depressed, very guilty afterwards at least once/wk x 3 mo
- not associated with any compensatory behaviours
- dieting usually follows binge-eating (vs. BN where dysfunctional dieting typically precedes binge-eating)
- associated with health consequences (i.e. increased risk of weight gain, obesity)

### Epidemiology
- F:M = 2:1
- begins in adolescence or young-adulthood

### Treatment
- CBT

# Avoidant/Restrictive Food Intake Disorder

## Definition

- eating/feeding disturbance to the extent of persistent failure to meet appropriate nutritional and/or energy needs, resulting in significant weight loss/growth failure and nutritional deficiencies; patients experience disturbances in psychosocial functioning and may become dependent on enteral feeding/oral nutritional supplementation
  - does not occur during an episode of AN or BN
  - no evidence of distress in the way in which one's body weight or shape is experienced

## Risk Factors

- temperament (i.e. anxiety disorders), environment (i.e. familial anxiety), genetic (i.e. history of GI conditions)
- begins in infancy and can persist into adulthood

## Treatment

- psychoeducation
- behaviour modification
- psychotherapy

**Points for Differentiating Between Eating Disorders**

- AN of binge-eating/purging type (significantly low body weight) takes priority over a BN diagnosis (body weight not in criteria)
- BN requires compensatory behaviours
- Binge eating disorder does not involve compensatory behaviours
- Avoidant/restrictive food intake disorder does not involve disturbances in body image

**Table 9. Physiologic Complications of Eating Disorders**

| System | Starvation/Restriction | Binge-Purge |
|---|---|---|
| **General** | Low BP, low HR, significant orthostatic changes ± syncopal episodes, low temperature, vitamin deficiencies | Russell's sign (knuckle callus)<br>Parotid gland enlargement<br>Perioral skin irritation<br>Periocular and palatal petechiae<br>Loss of dental enamel and caries<br>Aspiration pneumonia<br>Metabolic alkalosis secondary to hypokalemia and loss of acid |
| **Endocrine** | Primary or secondary amenorrhea, decreased $T_3/T_4$ | |
| **Neurologic** | Seizure (decreased $Ca^{2+}$, $Mg^{2+}$, $PO_4^{3-}$) | |
| **Cutaneous** | Dry skin, lanugo hair, hair loss or thinning, brittle nails, yellow skin from high carotene | |
| **GI** | Constipation, GERD, delayed gastric emptying | Acute gastric dilation/rupture, pancreatitis, GERD, hematemesis secondary to Mallory-Weiss tear |
| **CVS** | Arrhythmias, CHF | Arrhythmias, cardiomyopathy (from use of ipecac), sudden cardiac death (decreased $K^+$) |
| **MSK** | Osteoporosis secondary to hypogonadism | Muscle wasting |
| **Renal** | Pre-renal failure (hypovolemia), renal calculi | Renal failure (electrolyte disturbances) |
| **Extremities** | Pedal edema (decreased albumin) | Pedal edema (decreased albumin) |
| **Lab Values** | Starvation: decreased RBCs, decreased WBCs, decreased LH, decreased FSH, decreased estrogen, decreased testosterone, increased growth hormone, increased cholesterol<br>Dehydration: increased BUN | Vomiting: decreased $Na^+$, decreased $K^+$, decreased $Cl^-$, decreased $H^+$, increased amylase; hypokalemia with metabolic alkalosis<br>Laxatives: decreased $Na^+$, decreased $K^+$, decreased $Cl^-$, increased $H^+$; metabolic acidosis |

Important electrolytes in eating disorders: KPMg (potassium, phosphate, magnesium)

# Personality Disorders

- in the literature, personality and its disorders are better understood using a trait-based dimensional approach (i.e. 5 major traits such as extraversion, agreeableness, conscientiousness, neuroticism, and openness to experiences rated on a continuum of dysfunctional effects) rather than discrete categories; however, the discrete categories still remain in the current DSM and will be referenced here

## General Information

- an enduring pattern of inner experience and behaviour that deviates markedly from the expectations of the individual's culture; manifested in two or more of: cognition, affect, interpersonal functioning, impulse control
- inflexible and pervasive across a range of situations
- pattern is stable and well established by adolescence or early adulthood (vs. a sudden onset)
- associated with many complications, such as depression, suicide, violence, brief psychotic episodes, multiple drug use, and treatment resistance
- relationship building and establishing boundaries are important; focus should be placed on validating, finding things to be truly empathetic about, and speaking to the patient's strengths
- mainstay of treatment is psychotherapy, add pharmacotherapy to treat associated psychiatric disorders (i.e. depression, anxiety, substance abuse)

A flag for personality disorders in clinical setting is the reaction that a patient is eliciting in you

## Classification

- personality disorders are divided into three clusters (A, B, and C), with shared features among disorders within each

Personality disorders with familial associations: Schizotypal, Antisocial, and Borderline

## Table 10. Description and Diagnosis of Personality Disorders

**Cluster A "Mad" Personality Disorders**
- Patients seem odd, eccentric, withdrawn
- Familial association with psychotic disorders
- Common defense mechanisms: intellectualization, projection, magical thinking

**Paranoid Personality Disorder (0.5-3%)**
Pervasive distrust and suspiciousness of others, interpret motives as malevolent
Blame problems on others and seem angry and hostile
Diagnosis requires 4+ of: **SUSPECT**
1. **S**uspicious that others are exploiting or deceiving them
2. **U**nforgiving (bears grudges)
3. **S**pousal infidelity suspected without justification
4. **P**erceive attacks on character, counterattacks quickly
5. **E**nemies or friends? Preoccupied with acquaintance trustworthiness
6. **C**onfiding in others is feared
7. **T**hreats interpreted in benign remarks

**Schizotypal Personality Disorder (3-5.6%)**
Pattern of eccentric behaviours, peculiar thought patterns
Diagnosis requires 5+ of: **ME PECULIAR**
1. **M**agical thinking
2. **E**xperiences unusual perceptions (including body illusions)
3. **P**aranoid ideation
4. **E**ccentric behaviour or appearance
5. **C**onstricted or inappropriate affect
6. **U**nusual thinking/speech (e.g. vague, stereotyped)
7. **L**acks close friends
8. **I**deas of reference
9. **A**nxiety in social situations
(Note: Rule out psychotic/pervasive developmental disorders - this is not part of the criteria)

**Schizoid Personality Disorder**
Neither desires nor enjoys close relationships including being a part of a family; prefers to be alone. Lifelong pattern of social withdrawal. Seen as eccentric and reclusive with restricted affect
Diagnosis requires 4 of: **DISTANT**
1. **D**etached/flat affect, emotionally cold
2. **I**ndifferent to praise or criticism
3. **S**exual experiences of little interest
4. **T**asks done solitarily
5. **A**bsence of close friends (other than first-degree relatives)
6. **N**either desires nor enjoys close relationships (including family)
7. **T**akes pleasure in few (if any) activities

**Cluster B "Bad" Personality Disorders**
- Patients seem dramatic, emotional, inconsistent
- Familial association with mood disorders
- Common defense mechanisms: denial, acting out, regression (histrionic PD), splitting (borderline PD), projective identification, idealization/devaluation

**Borderline Personality Disorder (2-4%)**
Unstable moods and behaviour, feel alone in the world, problems with self-image. History of repeated suicide attempts, self-harm behaviours. Inpatients commonly report history of sexual abuse. Tends to fizzle out as patients age. DBT is the principal treatment (see *Psychotherapy*)
**10% suicide rate**
Diagnosis requires 5+ of: **IMPULSIVE**
1. **I**mpulsive (min. 2 self-damaging ways, e.g. sex/drugs/spending)
2. **M**ood/affect instability
3. **P**aranoia or dissociation under stress
4. **U**nstable self-image
5. **L**abile intense relationships
6. **S**uicidal gestures / self-harm
7. **I**nappropriate anger
8. a**V**oiding abandonment (real or imagined, frantic efforts to)
9. **E**mptiness (feelings of)

**Narcissistic Personality Disorder (2%)**
Sense of superiority, needs constant admiration, lacks empathy, but with fragile sense of self. Consider themselves "special" and will exploit others for personal gain
Diagnosis requires 5+ of: **GRANDIOSE**
1. **G**randiose
2. **R**equires excessive admiration
3. **A**rrogant
4. **N**eeds to be special (and associate with other specials)
5. **D**reams of success, power, beauty, love
6. **I**nterpersonally exploitative
7. **O**thers (lacks empathy, unable to recognize feelings/needs of)
8. **S**ense of entitlement
9. **E**nvious (or believes others are envious)

**Antisocial Personality Disorder (M: 3%, F: 1%)**
Lack of remorse for actions, manipulative and deceitful, often violate the law. May appear charming on first impression. Pattern of disregard for others and violation of others' rights must be present before age 15; however, for the diagnosis of ASPD patients must be at least 18. Strong association with Conduct Disorder, history of trauma/abuse common (see *Child Psychiatry*)
Diagnosis requires 3+ of: **CORRUPT**
1. **C**annot conform to law
2. **O**bligations ignored (irresponsible)
3. **R**eckless disregard for safety
4. **R**emorseless
5. **U**nderhanded (deceitful)
6. **P**lanning insufficient (impulsive)
7. **T**emper (irritable and aggressive)

**Histrionic Personality Disorder (1.3-3%)**
Attention-seeking behaviour and excessively emotional. Are dramatic, flamboyant, and extroverted. Cannot form meaningful relationships. Often sexually inappropriate
Diagnosis requires 5+ of: **ACTRESSS**
1. **A**ppearance used to attract attention
2. **C**entre of attention (else uncomfortable)
3. **T**heatrical
4. **R**elationships (believed to be more intimate than they are)
5. **E**asily influenced
6. **S**eductive behaviour
7. **S**hallow expression of emotions (which rapidly shift)
8. **S**peech (impressionistic and vague)

**Cluster C "Sad" Personality Disorders**
- Patients seem anxious, fearful
- Familial association with anxiety disorder
- Common defense mechanisms: isolation, avoidance, hypochondriasis

**Avoidant Personality Disorder (0.5-1.6%)**
Timid and socially awkward with a pervasive sense of inadequacy and fear of criticism. Fear of embarrassing or humiliating themselves in social situations so remain withdrawn and socially inhibited
Diagnosis requires 4+ of: **CRINGES**
1. **C**riticism or rejection preoccupies thoughts in social situations
2. **R**estraint in relationships due to fear of being shamed
3. **I**nhibited in new relationships due to fear of inadequacy
4. **N**eeds to be sure of being liked before engaging socially
5. **G**ets around occupational activities requiring interpersonal contact
6. **E**mbarrassment prevents new activity or taking risks
7. **S**elf-viewed as unappealing or inferior

**Obsessive-Compulsive Personality Disorder (3-10%)**
Preoccupation with orderliness, perfectionism, and mental and interpersonal control. Is inflexible, closed-off, and inefficient
Diagnosis requires 4+ of: **SCRIMPER**
1. **S**tubborn
2. **C**annot discard worthless objects
3. **R**ule/detail obsessed (to point of activity lost)
4. **I**nflexible in matters of morality, ethics, values
5. **M**iserly
6. **P**erfectionistic
7. **E**xcludes leisure due to devotion to work
8. **R**eluctant to delegate to others

**Dependent Personality Disorder (1.6-6.7%)**
Pervasive and excessive need to be taken care of, excessive fear of separation, clinging and submissive behaviours. Difficulty making everyday decisions. Useful to set regulated treatment schedule (regular, brief visits) and being firm about in between issues. Encourage patient to do more for themselves, engage in own problem-solving
Diagnosis requires 5 of: **RELIANCE**
1. **R**eassurance required for everyday decisions
2. **E**xpressing disagreement difficult
3. **L**ife responsibilities assumed by others
4. **I**nitiating projects difficult (because no confidence)
5. **A**lone (feels helpless and uncomfortable when alone)
6. **N**urturance (goes to excessive lengths to obtain)
7. **C**ompanionship sought urgently
8. **E**xaggerated fears of being left to care for self

**Table 11. Key Differences Among Schizoid, Schizotypal, and Schizophrenia**

| | Schizoid | Schizotypal | Schizophrenia |
|---|---|---|---|
| **Thought Form** | Organized | Organized, but vague and circumstantial | Disorganized, tangential, loosening of associations |
| **Thought Content** | No psychosis | No psychosis, may have ideas of reference, paranoid ideation, odd beliefs and magical thinking | Psychosis, hallucinations |
| **Relationships** | Solitary, NO desire for social relationships | Lacks close relationships, INTERESTED in relationships but socially inept | Socially marginalized, but not by choice |

**OCPD vs. OCD**

| | OCPD | OCD |
|---|---|---|
| **Ego-Syntonic or Ego-Dystonic** | Ego-syntonic | Ego-dystonic |
| **Thought Content** | Obsessional thinking, no compulsions, strict routine and rigidity in day-to-day matters, more perfectionistic and rigid | Obsessions and compulsions, rituals, anxiety provoking unwanted intrusive thoughts |

# Child Psychiatry

## Developmental Concepts

- temperament: a child's innate psycho-physiological and behavioural characteristics (i.e. emotionality, activity, and sociability); spectrum from "difficult" to "slow-to-warm-up" to "easy temperament"
- parental fit: the congruence between parenting style (authoritative, permissive) and child's temperament
- attachment: special relationship between child and primary caretaker(s); develops during first year, the caretaker's attachment style is the best predictor of their child's attachment style, refer to Table 12
- separation anxiety (normal between 10-18 mo): where separation from attachment figure results in distress

Consider speaking to children alone. Always consider child abuse in your ddx.
See Pediatrics, P15

**Table 12. Attachment Models**

| Parent/Caregiver | Attachment Type | Features in Child |
|---|---|---|
| Loving, consistently available, sensitive, and receptive | Secure | Freely explores and engages with strangers well (as long as mother in close proximity), upset with caregiver's departure, happy with return |
| Rejecting, unavailable psychologically, insensitive responses | Insecure (avoidant) | Ignores caregiver, shows little emotion with arrival or departure, little exploration |
| Inconsistent, insensitive responses, role reversal | Insecure (ambivalent/ resistant) | Clingy but inconsolable, often displays anger or helplessness, little exploration |
| Frightening, dissociated, sexualized, or atypical<br>Often history of trauma or loss | Disorganized | Simultaneous approach/avoidance and stress related straining behaviour |

**Tips for the Child Interview**
- Use language the child will understand (i.e. don't ask about feeling of worthlessness, ask about whether they feel like they're a bad kid)
- Children in some cultures are taught to be quiet and avoid eye contact with adults who are authority figures (do not mistake with depression)
- Use developmentally-appropriate questions (i.e. don't ask about lack of interest in activities, ask children whether they feel bored)

## Mood Disorders

### MAJOR DEPRESSIVE DISORDER

#### Epidemiology
- lifetime prevalence for pre-pubertal 1-2% (F:M = 1:1); adolescents 8-18% (F:M = 2:1)

#### Clinical Feature
- only difference in diagnostic criteria is that irritable mood may replace depressed mood
- physical features: insomnia (children), hypersomnia (adolescents), somatic complaints, substance abuse, decreased hygiene
- psychological features: irritability, boredom, anhedonia, low self-esteem, deterioration in academic performance, social withdrawal, lack of motivation, listlessness
- common comorbid diagnoses: anxiety, ADHD, ODD, conduct disorder,, and eating disorders

**HEEADSSS Interview**
**H**ome environment
**E**ducation/**E**mployment
**A**ctivities
**D**rugs/**D**iet
**S**ex
**S**afety
**S**uicide/depression

#### Treatment
- majority never seek treatment
- individual (CBT, IPT), family therapy and education, modified school program
- SSRIs: 1st line fluoxetine; 2nd line escitalopram, sertraline
- close follow-up for adolescents starting SSRIs to monitor for increased suicidal ideation or behaviour
- in severe depression, best evidence for combined pharmacotherapy and psychotherapy
- ECT: only in adolescents who have severe illness, psychotic features, catatonic features, persistently suicidal
- internet based psychotherapy, light therapy, self-help books and applications

#### Prognosis
- prolonged episodes, up to 1-2 yr = poor prognosis
- adolescent onset predicts chronic mood disorder; up to 2/3 will have another depressive episode within 5 yr
- complications: negative impact on family and peer relationships, school failure, significantly increased risk of suicide attempt (10%) or completion (however, suicide risk low for pre-pubertal children), substance abuse

### DISRUPTIVE MOOD DYSREGULATION DISORDER

#### Clinical Feature
- severe, developmentally inappropriate, recurrent verbal or behavioural temper outbursts at least 3x/wk with persistently irritable mood in between
- symptom onset before age 10, occurring for ≥ 12 mo, in ≥ 2 settings, with no more than 3 consecutive mo free from symptoms
- diagnosis should be made between 6 and 18 years of age
- criteria not met for intermittent explosive disorder, bipolar disorder (no mania/hypomania)
- supersedes diagnosis of ODD if criteria for both are met
- common comorbidities: ADHD, anxiety disorders, depressive disorders

### BIPOLAR DISORDER

#### Clinical Feature
- mixed presentation and psychotic symptoms (hallucinations and delusions) more common in adolescent population than adult population
- unipolar depression may be an early sign of adult bipolar disorder
- ~30% of psychotic depressed adolescents receive a bipolar diagnosis within 2 yr of presentation
- associated with rapid onset of depression, psychomotor retardation, mood-congruent psychosis, affective illness in family, and pharmacologically-induced mania

#### Treatment
- pharmacotherapy: mood stabilizers (lithium, anticonvulsants) and/or antipsychotics (risperidone, olanzapine, quetiapine, aripiprazole)
- psychotherapy: CBT, Family Focused Therapy

## Anxiety Disorders

- lifetime prevalence 10-20%; F:M = 2:1

#### Clinical Feature
- children and adolescents rarely vocalize their anxiety but instead exhibit behavioural manifestations
- associated with school problems, recurrent physical symptoms (abdominal pain, headaches) especially in mornings, social and relationship problems, social withdrawal and isolation, family conflict, difficulty with sleep initiation, temper tantrums, irritability and mood symptoms, alcohol and drug use in adolescents

#### Differential Diagnosis
- depressive disorders, ODD, truancy
- persistence and impairment to daily functioning differentiates anxiety disorder from normal anxiety
- for school avoidance, differentiate fear of general performance and humiliation
- consider anxiety about separation, and rule out bullying and school refusal due to learning disorder

#### Course and Prognosis
- better prognosis with later age of onset, fewer co-morbidities, early initiation of treatment, ability to maintain school attendance and peer relationships, and absence of social anxiety disorder
- with treatment, up to 80% of children will not meet criteria for their anxiety disorder at 3 yr follow-up, but up to 30% will meet criteria for another psychiatric disorder

#### Treatment
- similar principles for most childhood anxiety disorders due to overlapping symptomatology and frequent comorbidity
- family psychotherapy, predictive, and supportive environment
- CBT: child and parental education, relaxation techniques (i.e. deep breathing), exposure/desensitization, recognizing and correcting anxious thoughts
- pharmacotherapy: SSRIs (i.e. sertraline, fluoxetine)

### SEPARATION ANXIETY DISORDER
- excessive and developmentally inappropriate anxiety on real, threatened, or imagined separation from attachment figures or home, with physical or emotional distress for at least 4 wk
- persistent worry about losing attachment figures or experiencing an untoward event to self; reluctance to go places, be alone, or sleep alone; nightmares involving separation; physical symptoms when separated
- school refusal (75%) and comorbid major depression common (2/3)

### SOCIAL ANXIETY DISORDER (SOCIAL PHOBIA)
- anxiety, fear, and/or avoidance provoked by situations where child feels under the scrutiny of others
- must distinguish between shy child, child with issues functioning socially (i.e. autism), and child with social anxiety
  - diagnosis only if anxiety interferes significantly with daily routine, social life, academic functioning, or if markedly distressed. Must occur in settings with peers, not just adults
- features: crying, tantrums, freezing, clinging behaviour, mutism, excessively timid, stays on periphery, refuses to be involved in group play
- significant implication for future quality of life if untreated; lower levels of satisfaction in leisure activities, higher rates of school dropout, poor workplace performance, increased rates of remaining single



Attachment type can be assessed in infants 10-18 mo of age using the Strange Situation test, in which the child is stressed by the caregiver being removed from the situation and the stranger staying. Attachment style is measured by the child's behaviour during the reunion with the caregiver



Attachment problems may present as a child who is difficult to soothe, has difficulty sleeping, problems feeding, tantrums, or behavioural problems



The shy child is quiet and reluctant to participate but slowly 'warms up'

### SELECTIVE MUTISM
- consistent failure to speak in specific social situations where speaking is expected, despite speaking in other situations for ≥ 1 mo
- the disturbance interferes with educational or occupational achievement or with social communication
- not due to lack of knowledge of language or communication disorder

### GENERALIZED ANXIETY DISORDER
- diagnostic criteria same as adults (note: only 1 item is required in children for Criteria C)
- often redo tasks, show dissatisfaction with their work, and tend to be perfectionistic
- often fearful in multiple settings and expect more negative outcomes when faced with academic or social challenges, and require reassurance and support to take on new tasks

### SPECIFIC PHOBIA
- common phobias in childhood: fear of heights, small animals, doctors, dentists, darkness, loud noises, thunder, lightning

### OCD
- diagnostic criteria same as adults
- note: young children may not be able to articulate the aims of these behaviours or mental acts, i.e. compulsions

# Neurodevelopmental Disorders

## Autism Spectrum Disorder

### Diagnosis
- persistent deficits in social communication and interaction, manifested in three areas:
  - **social-emotional reciprocity**: abnormal social approach and failure of normal back-and-forth conversation; reduced sharing of interests, emotions, or affect; failure to initiate or respond to social interactions
  - **nonverbal communicative behaviours**: poorly integrated verbal and nonverbal communication; abnormalities in eye contact and body language or deficits in understanding and use of gestures; total lack of facial expressions and nonverbal communication
  - **developing, maintaining, and understanding relationships**: difficulties adjusting behaviour to suit various social contexts; difficulties in sharing imaginative play or in making friends; absence of interest in peers
- restricted, repetitive patterns of behaviour, interests, or activities: manifested by ≥2 of: stereotyped or repetitive motor movements, insistence on sameness, highly restricted fixated interests, hyper-/hypo-reactivity to sensory input
- symptoms must be present in early developmental period
- symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning
- not better explained by intellectual disability or global developmental delay
- specifiers
  - current severity: requiring very substantial support, requiring substantial support, requiring support
  - ± language impairment, ± intellectual impairment, ± catatonia
  - associated with known medical or genetic condition or environmental factor

### Differential Diagnosis
- neurodevelopmental: global delay, intellectual disability, language disorder, social communication disorder, learning disorder, developmental coordination disorder, stereotypic movement disorder
- mental and behavioural: ADHD, mood disorder, anxiety disorder, selective mutism, attachment disorder, ODD, conduct disorder, OCD, childhood schizophrenia,
- conditions with developmental regression: Rett syndrome, epileptic encephalopathy (Landau-Kleffner)
- other: hearing/visual impairment, abuse

### Treatment
- team-based: school, psychologist, occupational therapist, physiotherapist, speech language therapy, pediatrics, psychiatry
- psychosocial: family education and support, school programming, behavioural therapy, social skills training
- treat concomitant disorders such as ADHD, tics, OCD, anxiety, depression, and seizure disorder
- adjunctive pharmacotherapy (does not treat ASD itself): atypical antipsychotics (for irritability, aggression, agitation, self-mutilation, tics), SSRIs (for anxiety, depression), stimulants (for associated inattention and hyperactivity)

### Prognosis
- variable, but improves with early intervention
- better if IQ >60 and able to communicate



**Fluoxetine, Cognitive-Behavioural Therapy and Their Combination for Adolescents with Depression: Treatment for Adolescents with Depression Study (TADS) Randomized Controlled Trial**
JAMA 2004;292:807-820
**Purpose**: To evaluate effectiveness of fluoxetine alone, cognitive behavioural therapy (CBT) alone, CBT with fluoxetine and placebo among adolescents with major depressive disorder (MDD).
**Methods**: Randomized controlled trial at 13 US academic and community clinics between spring 2000-summer 2003, including patients aged 12-17 with a primary DSM IV diagnosis of MDD assigned to one of the aforementioned four treatment arms. The primary outcome was the Children's Depression Rating Scale-Revised (CDRSR) total score.
**Results**: Fluoxetine with CBT had a statistically significant CDRSR score as compared to placebo (p=0.001) with a 71% response rate. This combination was greater than fluoxetine alone (p=0.02), and CBT alone (p=0.01). Fluoxetine alone was greater than CBT alone (p=0.01).
**Conclusion**: Combination of fluoxetine with CBT offered the most favourable benefit-risk tradeoff for adolescents with MDD.



**Efficacy and Safety of Selective Serotonin Reuptake Inhibitors, Serotonin-Norepinephrine Reuptake Inhibitors, and Placebo for Common Psychiatric Disorders Among Children and Adolescents: A Systematic Review and Meta-Analysis**
JAMA Psychiatry. 2017 Oct 1;74(10):1011-1020
**Purpose**: Examine the relative efficacy and safety of SSRIs, SNRIs, and placebo for the treatment of depressive disorders (DDs), anxiety disorders (ADs), obsessive-compulsive disorder (OCD), and posttraumatic stress disorder (PTSD) in children and adolescents.
**Methods**: Meta-analysis of RCTs regarding use of SSRIs or SNRIs in youths with DD, AD, OCD, or PTSD. Effect sizes, calculated as standardized mean differences (Hedges g) and risk ratios (RRs) for adverse events, were assessed in a random-effects model.
**Results**: Thirty-six trials were eligible and analysis showed that SSRIs and SNRIs were more beneficial compared with placebo (g = 0.32; 95% CI, 0.25-0.40; P < .001). ADs (g = 0.56; 95% CI, 0.40-0.72; P < .001) had larger between-group effect sizes than DDs (g = 0.20; 95% CI, 0.13-0.27; P < .001). Patients with DDs exhibited significantly larger placebo responses (g = 1.57; 95% CI, 1.36-1.78; P < .001) compared with those with ADs (g = 1.03; 95% CI, 0.84-1.21; P < .001). The SSRIs produced a relatively large effect size for ADs (g = 0.71; 95% CI, 0.45-0.97; P < .001). Patients receiving an antidepressant versus a placebo reported significantly more treatment-emergent adverse events (RR, 1.07; 95% CI, 1.01-1.12; P = .01 or RR, 1.49; 95% CI, 1.22-1.82; P < .001, depending on the reporting method), severe adverse events (RR, 1.76; 95% CI, 1.34-2.32; P < .001), and study discontinuation due to adverse events (RR, 1.79; 95% CI, 1.38-2.32; P < .001).
**Conclusion**: Compared with placebo, SSRIs and SNRIs are more beneficial than placebo in children and adolescents; however, the benefit is small and disorder specific, yielding a larger drug-placebo difference for AD than for other conditions. Response to placebo is large, especially in DD. Severe adverse events are significantly more common with SSRIs and SNRIs than placebo.

# Attention Deficit Hyperactivity Disorder

- prevalence: 5-12% of school-aged children; M:F = 4:1, although girls may be under-diagnosed
- girls tend to have inattentive symptoms; boys tend to have impulsive/hyperactive symptoms

## Etiology

- genetic: 75% heritability, dopamine candidate genes DAT1, DRD4
- neurobiology: decreased catecholamine transmission, low prefrontal cortex (PFC) activity, increased beta activity on EEG
- cognitive: developmental disability, poor inhibitory control, and other errors of executive function

## Diagnosis

- diagnosis requires: onset before age 12, persistent symptoms ≥6 mo, symptoms present in ≥2 settings (i.e. home, school, work), interferes with academic, family, and social functioning, and is divided into 3 subtypes
  - combined type: ≥6 symptoms of inattention and ≥6 symptoms of hyperactivity-impulsivity
  - predominantly inattentive type: ≥6 symptoms of inattention
  - predominantly hyperactive-impulsive type: ≥6 symptoms of hyperactivity-impulsivity
  - for older adolescents and adults (≥ age 17), ≥5 symptoms required
- does not occur exclusively during the course of another psychiatric disorder
- differential: learning disorders, hearing/visual defects, thyroid, atopic conditions, congenital problems (fetal alcohol syndrome, Fragile X), lead poisoning, history of head injury, traumatic life events abuse)
- specify current severity (mild/moderate/severe); if in partial remission (past dx, has not met full criteria >6 mo, still functional impairment present)



**Observe child for "ATENTION" features**
**A**nnoying
**T**emperamental
**E**nergetic
**N**oisy
**T**ask incompletion
**I**nattentive
**O**ppositional
**N**egativism

**Table 13. Core Symptoms of ADHD (DSM-5)**

| Inattention | Hyperactivity | Impulsivity |
|---|---|---|
| Careless mistakes | Fidgets, squirms in seat | Blurts out answers before questions completed |
| Cannot sustain attention in tasks or play | Leaves seat when expected to remain seated | Difficulty awaiting turn |
| Does not listen when spoken to directly | Runs and climbs excessively | Interrupts/intrudes on others |
| Fails to complete tasks | Cannot play quietly | |
| Disorganized | "On the go", driven by a motor | |
| Avoids, dislikes tasks that require sustained mental effort | Talks excessively | |
| Loses things necessary for tasks or activities | | |
| Distractible | | |
| Forgetful | | |



**Comparative Efficacy and Tolerability of Medications for Attention-Deficit Hyperactivity Disorder in Children, Adolescents, and Adults: A Systematic Review and Network Meta-Analysis**
Lancet 2018;5:727-738.
**Objective**: Estimate the comparative efficacy and tolerability of oral medications for ADHD in children, adolescents, and adults.
**Methods**: Review of double-blind RCTs comparing amphetamines, atomoxetine, bupropion, clonidine, guanfacine, methylphenidate, and modafinil with each other or placebo.
**Conclusions**: Taking into account both efficacy and safety, evidence from this meta-analysis supports methylphenidate in children and adolescents, and amphetamines in adults, as preferred first-choice medications for the short-term treatment of ADHD.

## Features

- difficult to differentiate from highly variable normative behaviour before age 4, but often identified upon school entry
- rule out developmental delay, sensory impairments, genetic syndromes, encephalopathies or toxins (alcohol, lead)
- increased risk of substance abuse, depression, anxiety, academic failure, poor social skills, comorbid CD and/or ODD, adult ASPD
- associated with family history of ADHD, difficult temperamental characteristics



Treatment with stimulant medications of ADHD in childhood does not increase the likelihood of substance abuse later in life, contrary to the concerns of many parents and health care providers

## Treatment

- non-pharmacological: psychoeducation, behavioural management i.e. parent training, classroom management, social skills training
- pharmacological: 1st line stimulants (methylphenidate, amphetamines); 2nd line atomoxetine; 3rd line/adjunct nonstimulants (guanfacine, clonidine, buproprion)
- for comorbid symptoms: antidepressants, antipsychotics

## Prognosis

- 70-80% continue into adolescence, but hyperactive symptoms usually abate
- 65% continue into adulthood; secondary personality disorders and compensatory anxiety disorders are identifiable

# Disruptive, Impulse Control, and Conduct Disorder

## Oppositional Defiant Disorder

- prevalence: 2-16%, M=F after puberty

### Diagnosis

- pattern of negativistic/hostile and defiant behaviour for ≥6 mo, with ≥ 1 non-sibling, with ≥4 symptoms manifested in 3 areas of:
  - **angry/irritable mood**: easily loses temper, touchy or easily annoyed, often angry and resentful
  - **argumentative/defiant**: argues with adults/authority figure, defies requests/rules, deliberately annoys, blames others for their own mistakes or misbehaviour
  - **vindictiveness**: spiteful or vindictive twice in past 6 mo
  - note: difference between normal behaviour and ODD is frequency of symptoms (most days if age <5 yr, weekly if age ≥5 yr) exceeds what is normative for one's age gender, culture
- behaviour causes significant distress or impairment in social, academic, or occupational functioning
- behaviours do not occur exclusively during the course of a psychotic, substance use, or mood disorder
- diagnosis of disruptive mood dysregulation disorder supersedes ODD if criteria for both are met
- severity (mild/moderate/severe) according to number of settings in which symptoms are present



**ODD kids "ARE BRATS"**
**A**nnoying
**R**esentful
**E**asily annoyed
**B**lames others
**R**ule breaker
**A**rgues with adults
**T**emper
**S**piteful/vindictive

### Features

- first symptoms usually appear during preschool and rarely later than early adolescence
- associated with poor school performance, few friends, strained parent/child relationships, risk of developing mood disorders later on, often precedes CD

### Treatment

- parent: parent management training, psychoeducation for parents and family
- behavioural therapy: to teach, practice, and reinforce prosocial behaviour
- social: school/day-care interventions
- pharmacotherapy for comorbid disorders

## Conduct Disorder

- prevalence: 1.5-3.4% (M:F = 4-12:1)



**Conduct Disorder Diagnosis**

**TRAP**
**T**heft: breaking and entering, deceiving, non-confrontational stealing
**R**ule breaking: running away, skipping school, out late
**A**ggression: people, animals, weapons, forced sex
**P**roperty destruction

### Etiology

- parental/familial factors: parental psychopathology (i.e. ASPD, substance abuse), child-rearing practices (i.e. child abuse, discipline), low socioeconomic status (SES), family violence
- child factors: difficult temperament, ODD, learning problems, neurobiology

### Diagnosis

- pattern of behaviour that violates rights of others and age appropriate social norms with ≥3 criteria noted in past 12 mo and ≥1 in past 6 mo:
  - aggression to people and animals: bullying, initiating physical fights, use of weapons, forced sex, cruel to people and/or animals, stealing while confronting a person (i.e. armed robbery)
  - destruction of property: arson, deliberately destroying others' property
  - deceitfulness or theft: breaking and entering, conning others, stealing nontrivial items without confrontation
  - violation of rules: out all night before age 13, often truant from school before age 13, runaway ≥2 times at least overnight or for long periods of time
  - disturbance causes clinically significant impairment in social, academic, or occupational functioning
  - if ≥18 yr, criteria not met for ASPD
- diagnostic types
  - childhood-onset ( ≥1 criterion prior to age 10)
  - adolescent-onset (no criteria until age 10)
  - unspecified- onset (insufficient information)
  - mild, moderate, severe
- differential: ADHD, depression, head injury, substance abuse

### Treatment

- early intervention necessary and more effective; long-term follow-up required
- psychosocial: parent management training, anger replacement training, CBT, family therapy, education/employment programs, social skills training
- pharmacotherapy for comorbid disorders

### Prognosis

- poor prognostic indicators include: early-age onset, high frequency, variety of behaviours, pervasiveness (i.e. in home, school, community), comorbid ADHD, early sexual activity, substance abuse
- 50% of CD children become adult ASPD

# Intermittent Explosive Disorder

## Diagnosis

- recurrent behavioural outbursts representing a failure to control aggressive impulses in children age ≥6, manifested as either
  - verbal or physical aggression that does not damage others or property, occurring ≥2 times per wk for 3 mo
  - 3 outbursts involving physical damage to another person, animal or piece of property in the last 12 mo
- outbursts are out of proportion to triggers are not premeditated or for primary gain
- outbursts cause clinically significant distress or impairment in occupation or interpersonal functioning, or financial/legal consequences

## See Pediatrics

- *Child Abuse,* P15
- *Chronic Abdominal Pain,* P41
- *Developmental Delay,* P23
- *Intellectual Disability,* P23
- *Learning Disabilities,* P25
- *Sleep Disturbances,* P12

## See Neurology

- *Tic Disorders,* N33
- *Tourette's Syndrome,* N34

# Psychotherapy

- treatment in which a person with mental or physical difficulties aims to achieve symptomatic relief through interactions with another person
- psychotherapy is delivered by a trained counsellor, social worker, nurse, psychologist, general practitioner, or psychiatrist
- various types of therapy exist based on diverse theories of human psychology and mental illness etiology



**Freudian Psyche**
**id:** instinctual drives, unconscious
**superego:** person's conscience, formed by societal/parental norms
**ego:** latin "I", sense of self, conscious actions, attempts to satisfy drives of id within confines of reality and demands of superego

## Common Factors of Psychotherapy

- good evidence that effective psychotherapy creates observable changes in brain circuitry and connectivity, but these changes are different from those observed with successful pharmacologic and other treatment modalities
- studies suggest that up to 60-90% of therapy outcome is due to common factors with only 10-40% due to specific factors
- common factors are: warmth (unconditional positive regard), accurate empathy, genuineness, goodness of fit, relationship with provider predicts positive outcomes

**Table 14. Summary of Psychotherapeutic Modalities**

| Type | Indications | Approach, Technique and Theory | Ideal Candidates | Duration |
|---|---|---|---|---|
| **Psychoanalytic/ Psychodynamic** | Anxiety, obsessional thinking, conversion disorder, sexual dysfunction, depression | Theory: Exploration of meaning of early experiences and how they affect emotions and patterns of behaviour<br>Recollection (remembering), repetition (reliving with the therapist), working through (gaining insight)<br>Techniques: free association, dream interpretation, transference analysis | Psychologically minded, highly motivated, wish to understand selves and not just relieve symptoms<br>Able to withstand difficult emotions without fleeing or self-destructive acts<br>High level of function | Time intensive:<br>Psychoanalysis: 4-5 times/wk for 3-7 yr<br>Psychodynamically oriented therapy: 2-3 times/wk for fewer years |
| **Supportive** | Adjustment disorders, somatic symptoms and related disorders, severe psychotic or personality disorders | Ameliorate symptoms through behavioural or environmental restructuring to aid adaptation and facilitate coping<br>Help patients feel safe, secure, and encouraged | Individuals in crisis or with severe symptoms in acute or chronic settings<br>Low insight, low motivation, "weak" ego systems | Variable (single session to years, though often short-intermittent) |
| **Interpersonal** | Mood disorders | Focuses on how interpersonal relationships impact symptoms<br>4 key problem areas addressed: 1 grief and loss, 2. role transitions, 3. conflict, 4. interpersonal deficits<br>Break the interpersonal cycle: depression, self-esteem, social withdrawal | Individuals with depression or bipolar disorder with some insight and difficult social functioning<br>Absence of severe psychotic process, personality disorder, or comorbid substance abuse | Weekly sessions, 12-20 sessions |
| **Behavioural** | Most mental health disorders benefit from specific application of behavioural therapy (i.e. behavioural activation for depression; exposure therapy for phobias; contingency management for anorexia nervosa and substance use disorder) | Systematic Desensitization: mastering anxiety-provoking situations by approaching them gradually and in a relaxed state that limits anxiety<br>Flooding: confronting feared stimulus for prolonged periods until it is no longer frightening<br>Positive Reinforcement: strengthening behaviour and causing it to occur more frequently by rewarding it<br>Negative Reinforcement: causing behaviour to occur more frequently by removing a noxious stimulus when desired behaviour occurs<br>Extinction: causing a behaviour to diminish by not rewarding it<br>Punishment (aversion therapy): causing a behaviour to diminish by applying a noxious stimulus | Individuals with motivation to change and specific symptoms that are amenable to change<br>Absence of global areas of dysfunction such as personality disorder | Usually short term (weeks-months) |

**Table 14. Summary of Psychotherapeutic Modalities** (continued)

| Type | Indications | Approach, Technique and Theory | Ideal Candidates | Duration |
|---|---|---|---|---|
| **Cognitive Therapy** | Depression, anxiety, panic disorder, personality disorders, and somatoform disorders | Moods/emotions are influenced by one's thoughts and psychiatric disturbances are often caused by habitual errors in thinking<br>Therapy helps patient make explicit their inaccurate automatic thoughts and correct assumptions with a more balanced perspective<br>Uses thought records (often charts with column headings including "situation," "feeling," "thought," "cognitive distortion") to help monitor thoughts, the situations they occur in, and the feelings they might provoke due to underlying cognitive errors | Motivated individuals who will comply with homework, openness to changing core beliefs | First course - weekly or twice weekly sessions, 12-20 sessions<br>Maintenance therapy can be carried out over years |
| **Cognitive Behavioural Therapy** | Most mental health disorders including; mood, anxiety, OCD, personality, eating, substance use, psychotic disorders | Combines theory and method from Cognitive and Behavioural therapies to teach the patient to change connections between thinking patterns, habitual behaviours, and mood/anxiety problems | Individuals with motivation to change and are able to participate in homework | Typically weekly or twice weekly sessions, 12-20 sessions<br>Maintenance therapy can be carried out over years |
| **Dialectical Behavioural Therapy** | Borderline Personality Disorder | Therapy that combines CBT techniques with Buddhist Zen mindfulness practices and dialectical philosophy<br>Focuses on 4 types of skills: mindfulness, emotion regulation, interpersonal effectiveness, and distress tolerance<br>Involves 4 components: individual therapy, group skills training, phone consultations, and a consultation team | Individuals with borderline personality disorder or borderline personality trait and severe problems of emotional dysregulation, impulsivity, or self-harm | Typically 1 yr<br>Weekly individual and group therapy |
| **Motivational Interviewing (MI) and Motivational Enhancement Therapy (MET)** | Substance use disorders<br>Techniques can be applied to facilitate behavioural change in most psychological problems | Spirit of MI (CAPE): Compassion, Acceptance, Partnership, Evocation<br>Principles of MI (RULE): Resist "righting reflex", Understand client and their reasons for change, Listen, Empower by conveying hope and supporting autonomy<br>Techniques of MI (OARS): Open-ended questions, Affirmations to validate client, Reflections (the skill of accurate empathy), Summaries to help client organize self | Individuals with problematic substance use, maladaptive behaviour patterns (therapy disengagement, medication noncompliance, poor health habits) | Brief interventions (efficacy with as little as 15 min, single session), better result with more sessions<br>Addiction is a chronic condition, often need boosters over time<br><br>MET = 4 sessions |

## Other Therapies

- group psychotherapy
  - aims to promote self-understanding, acceptance, social skills
- family therapy
  - family system considered more influential than individual, especially for children
  - focus on here and now, re-establishing parental authority, strengthening normal boundaries, and rearranging alliances
- mindfulness-based cognitive therapy (MBCT)/stress reduction (MBSR)
  - derived from Buddhist meditative and philosophical practices; aims to help people attend to thoughts, behaviours, and emotions in the moment and non-judgmentally using guided breathing exercises. Emerging evidence for treating adjustment disorder, MDD, anxiety, pain disorders, insomnia, substance relapse prevention
- narrative psychotherapy
  - an integrative approach that attempts to understand the patient's experience as a whole
- hypnosis
  - mixed evidence for treatment of pain, phobias, anxiety, and smoking cessation

# Pharmacotherapy

## Antipsychotics

- "antipsychotics" used to be called "neuroleptics"
- overall mechanism of action: block, to varying degrees, DA activity in target brain pathways
- primarily indicated for psychotic symptoms in: schizophrenia and related disorders, manic episodes, depressive episodes, substance use, medical conditions (i.e. neoplasm)
- other uses: treatment-resistant MDD, severe GAD, complex PTSD, severe OCD, borderline PD, behavioural symptoms of dementia, delirium, Tourette Syndrome, substance abuse in dual diagnosis, Huntington's disease, ASD, impulse control disorders
  - adjunctive management of agitation, aggression, severe anxiety, severe sleep difficulties when sedative-hypnotics are contraindicated
- onset: rapid calming effect and decrease in agitation; thought disorder responds in 1-4 wk
- rational use
  - no reason to combine two or more antipsychotics
  - all antipsychotics are equally effective, except for clozapine (considered to be most effective in treatment-refractory psychosis)

**Dopamine Pathways Affected by Antipsychotics**

| Pathway | Effects | Associated Pathology |
|---|---|---|
| Mesolimbic | Emotion origination, reward | HIGH dopamine causes positive symptoms of schizophrenia (delusions, hallucinations) |
| Mesocortical | Cognition, executive function | LOW dopamine causes negative symptoms of schizophrenia |
| Nigrostriatal | Movement | LOW dopamine causes EPS |
| Tuberoinfundibular | Prolactin hormone release | LOW dopamine causes hyperprolactinemia |

  - atypical antipsychotics (second generation) are as effective as typical (first generation) antipsychotics but are thought to have better adverse effect profiles; main difference is lower risk of EPS and TD (see sidebar)
  - choose a drug to which the patient has responded to in the past or that was used successfully in a family member
- route: PO, short-acting or long-acting depot IM injections, sublingual
- if no response in 4-6 wk, switch drugs
- duration: minimum 6 mo and usually for life in most patients with primary psychotic disorders; variable for other indications

### Long-Acting Preparations
- antipsychotics formulated in oil for IM injection
- received on an outpatient basis
- indications: individuals with schizophrenia or other chronic psychosis who relapse because of non-adherence
- should have been exposed to oral form prior to first injection
- dosing: start at low dosages, then titrate every 2-4 wk to maximize safety and minimize side effects
- side effects: risk of EPS, parkinsonism, increased risk of NMS

### Canadian Guidelines for the Treatment of Acute Psychosis in the Emergency Setting
- haloperidol 5 mg IM ± lorazepam 2 mg IM
- loxapine PO 25 mg ± lorazepam 2 mg IM
- olanzapine 2.5-10 mg (PO, IM, quick dissolve)
- risperidone 2 mg (M-tab, liquid)

**Table 15. Common Antipsychotic Agents**

| | Starting Dose | Maintenance | Maximum | Relative Potency (mg) |
|---|---|---|---|---|
| **Typicals** (in order of potency from high to low) | | | | |
| Haloperidol (Haldol®) | 2-5 mg IM q4-8h<br>0.5-5 mg PO b/tid<br>0.2 mg/kg/d PO | Based on clinical effect | 20 mg/d PO | 2 |
| | Based on clinical effect | 20 mg/d PO | 2 | |
| Fluphenazine enanthate (Moditen®, Modecate® for IM formulation) | 2.5-10 mg/d PO | 1-5 mg PO qhs<br>25 mg IM/SC q1-3wk | 20 mg/d PO | 2 |
| Zuclopenthixol HCl (Clopixol®) | 20-30 mg/d PO | 20-40 mg/d PO | 100 mg/d PO | 4 |
| Zuclopenthixol acetate (Acuphase®) | 50-150 mg IM q48-72h | | 400 mg IM (q2wk) | |
| Zuclopenthixol decanoate (Cloxipol Depot®) | 100 mg IM q1-4wk | 150-300 mg IM q2wk | 600 mg IM/wk | |
| Perphenazine (Trilafon®) | 8-16 mg PO b/tid | 4-8 mg PO t/qid | 64 mg/d PO | 10 |
| Loxapine HCl (Loxitane®) | 10 mg PO tid<br>12.5-50 mg IM q4-6h | 60-100 mg/d PO | 250 mg/d PO | 10 |
| Chlorpromazine (Largactil®) | 10-25 mg PO b/t/qid | 400 mg/d PO | 1000 mg/d PO | 100 |
| **Atypicals** (in order of potency from high to low) | | | | |
| Risperidone (Risperdal®, Risperdal Consta® for IM long acting preparation, Risperdal® M-Tab for melting form – placed on tongue) | 1-2 mg OD/bid | 4-8 mg/d PO<br>25 mg IM q2wk | 8 mg/d PO | 2 |
| Paliperidone (Invega®) | 3 mg/d PO | 3-12 mg /d PO | 12 mg/d PO | 4 |
| Olanzapine (Zyprexa®, Zyprexa Zydis® for melting form – placed on tongue, Zyprexa Intramuscular®) | 5 mg/d PO | 10-20 mg/d PO | 30 mg/d PO | 5 |
| Asenapine (Saphris®) | 5 mg SL bid | 5-10 mg SL bid | 10 mg bid | 5 |
| Ziprasidone (Zeldox®) | 20 mg bid PO | 40-80 mg bid PO | 160 mg/d PO | 6 |
| Aripiprazole (Abililfy®) | 10-15 mg/d PO | 10-15 mg/d PO | 30 mg/d PO | 7.5 |
| Quetiapine (Seroquel®, Seroquel XR® for extended release®) | 25 mg PO bid | 400-800 mg/d PO | 800 mg/d PO | 75 |
| Clozapine (Clozaril®) | 25 mg PO bid | 300-600 mg/d PO | 600 mg/d PO | 100 |

**Typical (First Generation) vs. Atypical (Second Generation) Antipsychotics**

| | Typical | Atypical |
|---|---|---|
| **Mechanism** | Block postsynaptic dopamine receptors (D2) | Block postsynaptic dopamine receptors (D2)<br>Block serotonin receptors (5-HT2) on presynaptic dopaminergic terminals, triggering DA release, and reversing DA blockade in some pathways |
| **Pros** | Inexpensive<br>Plenty of injectable forms available | Fewer EPS<br>Low risk of tardive syndromes<br>Mood stabilizing effects |
| **Cons** | More EPS<br>Tardive syndromes in long-term<br>Not mood stabilizing | Expensive<br>Few injectable forms available<br>Metabolic side effects (weight gain, hyperglycemia, lipid abnormalities, metabolic syndrome)<br>Exacerbation (or new onset) of obsessive behaviour |

**Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia**
New Engl J Med 2005;353:1209-23
**Purpose**: To compare perphenazine with several newer drugs (olanzapine, quetiapine, risperidone, ziprasidone) in patients with chronic schizophrenia.
**Methods**: Randomized, double-blind, active-control trial with median follow-up of 6 mo, involving patients with a diagnosis of schizophrenia (as per DSM-IV criteria) and able to take antipsychotic medications (as determined by study doctors). Patients were assigned to receive 1-4 capsules daily of olanzapine (20.1 mg), quetiapine (543.4 mg), risperidone (3.9 mg), perphenazine (20.8 mg), or ziprasidone (112.8 mg), with dosage at the discretion of the study doctor. Main outcome was discontinuation of treatment for any cause.
**Results**: 1432 patients were included. The olanzapine group had statistically significant lower rate of discontinuation for any cause (64%) from all others (quetiapine – 82%, risperidone – 74%, perphenazine – 75%, ziprasidone – 79%). There were no significant differences in time until discontinuation due to intolerable side effects; however, olanzapine was associated with a significantly higher rate of metabolic side effects.
**Conclusion**: The majority of patients in each group discontinued treatment due to inefficacy and intolerable side-effects, or for other reasons. Olanzapine was most effective in terms of lowest rates of discontinuation. Efficacy of conventional antipsychotic agent perphenazine was similar to quetiapine, risperidone and ziprasidone.

Note: high potency antipsychotics (i.e. haloperidol) have low doses, while low potency antipsychotics (i.e. chlorpromazine) have high doses

**Anticholinergic Effects**

| | | |
|---|---|---|
| **Red** | as a | beet |
| **Hot** | as a | hare |
| **Dry** | as a | bone |
| **Blind** | as a | bat |
| **Mad** | as a | hatter |

**Table 16. Commonly Used Atypical Antipsychotics**

| | Risperidone (Risperdal®) | Olanzapine (Zyprexa®, Zydis®) | Quetiapine (Seroquel®) | Clozapine (Clozaril®) | Aripiprazole (Abilify®) |
|---|---|---|---|---|---|
| **Advantages** | Lower incidence of EPS than typical antipsychotics at lower doses (<8 mg)<br>Associated with less weight gain compared to clozapine and olanzapine | Better overall efficacy compared to haloperidol<br>Well tolerated<br>Low incidence of EPS and TD | Associated with less weight gain compared to clozapine and olanzapine<br>Mood stabilizing | Most effective for treatment-resistant schizophrenia<br>Does not worsen tardive symptoms; may treat them<br>Approximately 50% of patients benefit, especially paranoid patients and those with onset after 20 yr | Less weight gain and risk of metabolic syndrome compared to olanzapine and a lower incidence of EPS compared to haloperidol<br>mood stabilizing |
| **Disadvantages relative to other SGAs** | Highest risk of EPS/TD among SGAs – avoid if high risk for EPS or existing movement disorder or elderly<br>Elevated prolactin - sexual dysfunction, galactorrhea, gynecomastia, menstrual disturbance, infertility | Weight gain and metabolic effects – avoid in DM<br>Sedating – avoid if high risk for falls or fracture | Sedating/ortho hypotension – avoid if high risk for falls or fracture<br>QT prolongation in high doses – caution if cardiac risk | Weight gain and metabolic effects- avoid in DM<br>Sedating/ortho hypotension - avoid if high risk for falls or fracture<br>Potentially severe constipation - avoid if risk of fecal impaction or bowel perforation<br>Cardiomyopathy – caution if existing heart disease<br>Seizures – caution if seizure disorder<br>Agranulocytosis (1%) – avoid in existing leukopenia/ neutropenia | Insomnia, akathisia |
| **Comments** | Quick dissolve (M-tabs), and long-acting (Consta®) formulations available | Quick dissolve formulation (Zydis®) used commonly in ER setting for better compliance<br>IM form available | | Weekly blood counts for 6 mo, then q2wk<br>Do not use with other drugs that may cause bone marrow suppression due to risk of agranulocytosis | |

Note: Risk of weight gain: Clozapine > Olanzapine > Quetiapine > Risperidone

**Metabolic and Cardiovascular Adverse Effects Associated with Antipsychotic Drugs**
Nat Rev Endocrinol 2012;8:114-126
All antipsychotics can cause cardiovascular and metabolic side effects, such as obesity, dyslipidemia, hyperglycermia and metabolic syndrome. Olanzapine and clozapine are most likely to cause these adverse effects. The mechanism that underlies the metabolic and cardiovascular effects is not fully understood, however, the histamine, dopamine, serotonin, and muscarinic receptors are implicated.

QTc prolongation is an important adverse effect of all antipsychotics; consider getting ECG prior to and after initiating new medication and to monitor QTc
**Typicals**: chlorpromazine and haloperidol warrant systematic baseline and follow-up ECG
**Atypicals**: ziprasidone has the highest risk among atypicals, clozapine also warrants systematic baseline and follow-up ECG

**Table 17. Side Effects of Antipsychotics**

| System | Side Effects |
|---|---|
| **Anticholinergic** | Dry mouth, urinary retention, constipation, blurred vision, confusional states |
| **β-adrenergic Blockade** | Orthostatic hypotension, erectile dysfunction, failure to ejaculate |
| **Dopaminergic Blockade** | Extrapyramidal syndromes, galactorrhea, amenorrhea, erectile dysfunction, weight gain |
| **Anti-histamine** | Sedation, weight gain |
| **Hematologic** | Agranulocytosis (clozapine) |
| **Hypersensitivity Reactions** | Liver dysfunction, blood dyscrasias, skin rashes, neuroleptic malignant syndrome, altered temperature regulation (hypothermia or hyperthermia) |
| **Endocrine** | Metabolic syndrome |

## Neuroleptic Malignant Syndrome

- psychiatric emergency
  - due to strong DA blockade; increased incidence with high potency and depot antipsychotics
- risk factors
  - medication factors: sudden increase in dosage, starting a new drug
  - patient factors: medical illness, dehydration, exhaustion, poor nutrition, external heat load, male, young adults
- clinical feature
  - tetrad: mental status changes (usually occur first), fever, rigidity, autonomic instability
  - develops over 24-72 h
  - labs: increased creatine phosphokinase, leukocytosis, myoglobinuria
- treatment: supportive - discontinue antipsychotic drug, hydration, cooling blankets, dantrolene (hydrantoin derivative, used as a muscle relaxant), bromocriptine (DA agonist)
- mortality: 5%

## Extrapyramidal Symptoms

- incidence related to increased dose and potency
- acute (early-onset; reversible) vs. tardive (late-onset; often irreversible)

**Table 18. Extrapyramidal Symptoms**

| | Dystonia | Akathisia | Pseudoparkinsonism | Dyskinesia |
|---|---|---|---|---|
| **Acute or Tardive** | Both | Both | Acute | Tardive |
| **High Risk Groups** | Acute: Young Asian and Black males | Older females | Older females | Older patients |
| **Presentation** | Sustained abnormal posture; torsions, twisting, contraction of muscle groups; muscle spasms (i.e. oculogyric crisis, laryngospasm, torticollis) | Motor restlessness; crawling sensation in legs relieved by walking; very distressing, increased risk of suicide and poor adherence | Tremor; rigidity (cogwheeling); akinesia; postural instability (decreased/absent arm-swing, stooped posture, shuffling gait, difficulty pivoting) | Purposeless, constant movements, involving facial and mouth musculature; less commonly – the limbs; rarely, the diaphragm ("hiccups") |
| **Onset** | Acute: within 5 d Tardive: >90 d | Acute: within 10 d Tardive: >90 d | Acute: within 30 d | Tardive: >90 d |
| **Treatment** | Acute: benztropine or diphenhydramine | Acute: lorazepam, propranolol, or diphenhydramine; reduce dose or change antipsychotic to lower potency | Acute: benztropine; reduce dosage or change antipsychotic to low potency atypical antipsychotic | Tardive: no good treatment; may try clozapine; discontinue drug or reduce dosage |

### Anticholinergic Agents

- types
  - benztropine (Cogentin®) 2 mg PO, IM, or IV OD (1-6 mg)
  - diphenhydramine (Benadryl®) 25-50 mg PO/IM qid
- do not routinely prescribe with antipsychotics
  - give anticholinergic agents only if at high risk for acute EPS or if acute EPS develops
- do not give these for tardive syndromes because they worsen the condition

## Antidepressants

- onset of effect
  - relief of neuro-vegetative/physical symptoms: 1-3 wk
  - relief of emotional/cognitive symptoms: 2-6 wk
- tapering of most antidepressants is usually required to avoid withdrawal reactions; speed of taper is based on the medication's half-life and the patient's individual sensitivity (i.e. fluoxetine does not require a taper due to its long half-life; paroxetine and venlafaxine require a slower taper than sertraline or citalopram)
- must be vigilant over the first 2 wk of therapy; neuro-vegetative symptoms may start to resolve while emotional and cognitive symptoms may not (patients may be at risk for suicidal behaviour during this time in particular children/adolescents)
- treatment of bipolar depression
  - patients with bipolar disorder should only be treated with an antidepressant if combined with a mood stabilizer or antipsychotic; monotherapy with antidepressants is not advisable as the depression can switch to mania

**Comparative Efficacy and Acceptability of 21 Antidepressant Drugs for the Acute Treatment of Adults with Major Depressive Disorder: A Systematic Review and Network Meta-Analysis**
Lancet 2018 Feb 20. pii: S0140-6736(17)32802-7
**Purpose**: Update of literature to compare and rank antidepressants for the acute treatment of adults with unipolar major depressive disorder (MDD).
**Methods**: Systematic review and network meta-analysis of RCTs.
**Results**: 522 trials were identified comprising 116 477 participants. All antidepressants were more effective than placebo, with ORs ranging between 2.13 (95% credible interval [CrI] 1.89-2.41) for amitriptyline and 1.37 (1.16-1.63) for reboxetine. For acceptability, only agomelatine (OR 0.84, 95% CrI 0.72-0.97) and fluoxetine (0.88, 0.80-0.96) were associated with fewer dropouts than placebo, whereas clomipramine was worse than placebo (1.30, 1.01-1.68). When all trials were considered, differences in ORs between antidepressants ranged from 1.15 to 1.55 for efficacy and from 0.64 to 0.83 for acceptability. In head-to-head studies, agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine were more effective than other antidepressants (range of ORs 1.19-1.96), whereas fluoxetine, fluvoxamine, reboxetine, and trazodone were the least efficacious drugs (0.51-0.84). For acceptability, agomelatine, citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine were more tolerable than other antidepressants (range of ORs 0.43-0.77), whereas amitriptyline, clomipramine, duloxetine, fluvoxamine, reboxetine, trazodone, and venlafaxine had the highest dropout rates (1.30-2.32), 46 (9%).
**Conclusion**: All antidepressants were more efficacious than placebo in adults with MDD. Smaller differences between active drugs were found when placebo-controlled trials were included in the analysis.

**Table 19. Common Antidepressants**

| Class | Drug | Daily Starting Dose (mg) | Therapeutic Dose (mg) | Comments |
|---|---|---|---|---|
| **SSRI** | fluoxetine (Prozac®)<br>fluvoxamine (Luvox®)<br>paroxetine (Paxil®)<br>sertraline (Zoloft®)<br>citalopram (Celexa®)<br>escitalopram (Cipralex®) | 20<br>50-100<br>10<br>50<br>20<br>10 | 20-80<br>150-300<br>20-60<br>50-200<br>20-40<br>10-20 | Useful for typical and atypical depression, seasonal depression, anxiety disorders, OCD, eating disorders<br>All SSRIs have similar effectiveness but consider side effect profiles and half-lives<br>Citalopram, and escitalopram have the fewest drug-interactions and are sleep-wake neutral<br>Sertraline is the safest SSRI in pregnancy and breastfeeding<br>Fluoxetine is the most activating SSRI (recommend taking in the AM)<br>Fluoxetine does not require a taper due to long half-life and is the most used in children as it has most evidence<br>Fluvoxamine is sedating (should be taken in PM) and can be involved in many drug-drug interactions |
| **SNRI** | venlafaxine (Effexor®)<br>Desvenlafaxine (Pristiq®)<br>duloxetine (Cymbalta®) | 37.5-75<br>50<br>30 | 75-225<br>50-100<br>30-60 | Useful for depression, anxiety disorders, neuropathic pain |
| **NDRI** | bupropion (Wellbutrin®) | 100 | 300-450 | Useful for depression, seasonal depression; not recommended for anxiety disorder treatment because of stimulating effects<br>Causes less sexual dysfunction (may reverse effects of SSRIs/SNRIs), weight gain, and sedation<br>Increased risk of seizures at higher doses<br>Contraindicated with history of seizure, stroke, brain tumour, brain injury, closed head injury<br>Important to specify formulation, as available in IR, SR, XL (longest) |
| **TCA (3º Amines)** | amitriptyline (Elavil®)<br>imipramine (Tofranil®) | 75-100<br>75-100 | 150-300<br>150-300 | Useful for OCD (clomipramine), melancholic depression; requires ECG monitoring; check blood levels if using higher dosage; highly lethal in overdose |
| **TCA (2º Amines)** | nortriptyline (Aventyl®)<br>desipramine (Norpramin®) | 75-100<br>100-200 | 75-150<br>150-300 | Preferred to tertiary amines because of lower propensity for anticholinergic adverse effects, requires ECG monitoring; check blood levels if using higher dosage; highly lethal in overdose |
| **MAOI** | phenelzine (Nardil®)<br>tranylcypromine (Parnate®) | 45<br>30 | 60-90<br>10-60 | Useful for moderate/severe depression that does not respond to other antidepressants, atypical depression; requires strict adherence to MAOI diet |
| **RIMA** | moclobemide (Manerix®) | 300 | 300-600 | Useful for depression that does not respond to other antidepressants |
| **NASSA** | mirtazapine (Remeron®) | 15 | 15-45 | Useful in depression with prominent features of insomnia, agitation, or cachexia |

MAOI = monoamine oxidase inhibitors; NASSA = noradrenergic and specific serotonin antagonists; NDRI = norepinephrine and dopamine reuptake inhibitors;
RIMA = reversible inhibition of MAO-A; SNRI = serotonin and norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants

## Treatment Approach for Depression

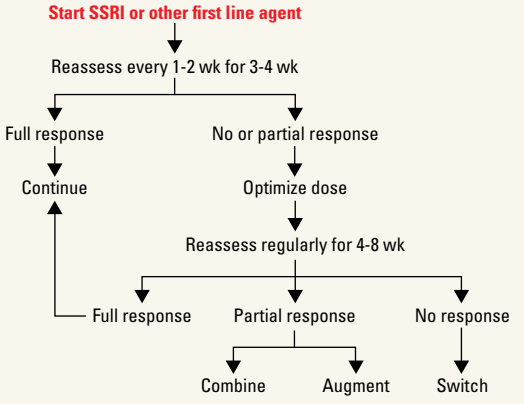



**Figure 3. Depression Treatment Algorithm**

- **optimization**: increase dosage to maximum tolerated or highest therapeutic dosage
- **augmentation**: the addition of a medication that is not considered an antidepressant to an antidepressant regimen (i.e. thyroid hormone, lithium, atypical antipsychotics [aripiprazole, quetiapine, olanzapine, risperidone])
- **combination**: the addition of another antidepressant to an existing treatment regimen (i.e. the addition of bupropion or mirtazapine to an SSRI or SNRI)
- switch: change of the primary antidepressant (within or outside a class)
- note: it is important to fully treat depression symptoms (i.e. to remission) to decrease relapse rates

**Psychopharmacology of SSRIs**

| Post-Synaptic Serotonin Receptor Stimulated | Effect/Side Effect |
|---|---|
| 5HT1A centrally | • Relief of depression<br>• Anxiolytic effect |
| 5HT2A in spinal cord | • Sexual dysfunction: delayed ejaculation, anorgasmia, decreased interest/ libido |
| 5HT2C/5HT2A in brain | • Activation: anxiety, insomnia<br>• Worst with fluoxetine, paroxetine<br>• Warn patients anxiety may worsen in first 1-2 wk of treatment |
| 5HT3A in gut | • GI upset: nausea, vomiting, bloating<br>• Take with food |

**Table 20. Features of Commonly Used Antidepressant Classes**

| | SSRI | SNRI | TCA | MAOI | NDRI | RIMA | NASSA |
|---|---|---|---|---|---|---|---|
| **Examples** | Fluoxetine, Sertraline, Citalopram | Venlafaxine, Duloxetine | Amitriptyline, Clomipramine | Phenelzine | Buproprion | Moclobemide | Mirtazapine |
| **Mode of Action** | Block serotonin reuptake only | Block norepinephrine and serotonin reuptake | Block norepinephrine reuptake (clomipramine also blocks serotonin reuptake) | Irreversible inhibition of monoamine oxidase A and B increases duration that NE and 5HT are in the synaptic cleft by preventing their degradation | Block norepinephrine and dopamine reuptake | Reversible inhibitor of monoamine oxidase A leads to increased duration NE and 5HT are in the synaptic cleft by preventing their degradation | Enhance central noradrenergic and serotonergic activity by inhibiting presynaptic α-2 adrenergic receptors |
| **Side Effects** | Fewer than TCA, therefore increased compliance<br>CNS: restlessness, tremor, insomnia, headache, drowsiness<br>GI: N/V, diarrhea, abdominal cramps, Weight gain<br>Sexual dysfunction: erectile dysfunction, anorgasmia<br>CVS: increased HR, Serotonin syndrome<br>SIADH, EPS | ow dose side effects similar to SSRIs (serotonergic)<br>Higher dose side effects: tremors, tachycardia, sweating, insomnia, orthostatic hypotension, increase in BP (noradrenergic)<br>SIADH | Anticholinergic effects: (see Table 17, PS46)<br>Noradrenergic effects: tremors, tachycardia, sweating α-1 adrenergic effects: orthostatic hypotension, falls<br>QRS prolongation | Antihistamine effects: sedation, weight gain<br>CVS: orthostatic hypotension, hypertensive crises with tyramine rich foods (i.e. wine, cheese):, headache, flushes, reflex tachycardia, postural hypotension, sedation, insomnia, weight gain<br>Minimal anticholinergic and antihistamine effects | CNS: dizziness, headache, tremor, insomnia<br>CVS: dysrhythmia, HTN<br>GI: dry mouth, N/V, constipation, decreased appetite<br>Other: agitation, anxiety | CNS: dizziness, headache, tremor, insomnia<br>CVS: dysrhythmia, hypotension<br>GI: dry mouth, N/V, diarrhea, abdominal pain, dyspepsia<br>GU: delayed ejaculation<br>Other: diaphoresis | CNS: sedation, dizziness<br>Endocrine: increase in cholesterol, triglycerides. weight gain<br>GI: constipation, ALT |
| **Risk in Overdose** | Relatively safe in OD | Tachycardia and N/V seen in acute overdose | Toxic in OD<br>3 times therapeutic dose may be lethal<br>Presentation: anticholinergic effects, CNS stimulation, then depression and seizures<br>ECG: prolonged QRS and QTc (reflect severity)<br>Treatment: activated charcoal, cathartics, supportive treatment, IV diazepam for seizure, physostigmine salicylate for coma<br>Do not give ipecac, as can cause rapid neurologic deterioration and seizures | Toxic in OD, but wider margin of safety than TCA | Tremors and seizures seen in overdose | Risk of fatal overdose when combined with SSRIs, SNRIs or clomipramine | Relatively safe in OD |
| **Drug Interactions** | MAOI, SNRI<br>Some SSRIs (fluoxetine, fluvoxamine, paroxetine) strongly inhibit cytochrome P450 enzymes, therefore will affect levels of drugs metabolized by P450 system | MAOI, SSRI<br>Low inhibition of cytochrome P450 compounds | MAOI, SSRI<br>EtOH | Hypertensive crises with noradrenergic medications (i.e. TCA, decongestants, amphetamines)<br>Serotonin syndrome with serotonergic drugs (i.e. SSRI, SNRI, tryptophan, dextromethorphan) | MAOI<br>Drugs that reduce seizure threshold: antipsychotics, systemic steroids, quinolone antibiotics, antimalarial drugs | MAOI, paroxetine<br>Opioids | MAOI, RIMA |

### Serotonin Syndrome
- thought to be due to over-stimulation of the serotonergic system
- can result from medication combinations such as SSRI+SNRI, SSRI or SNRI +MAOI, SSRI+tryptophan, MAOI+meperidine, MAOI+tryptophan
- rare but potentially life-threatening adverse reaction to SSRIs and SNRIs
- symptoms include: nausea, diarrhea, palpitations, chills, diaphoresis, restlessness, confusion, and lethargy but can progress to myoclonus, hyperthermia, rigor, and hypertonicity
- treatment: discontinue medication and administer emergency medical care as needed
- important to distinguish from NMS

### Discontinuation Syndrome
- caused by the abrupt cessation of some antidepressants; most commonly with paroxetine, fluvoxamine, and venlafaxine (drugs with shortest half-lives)
- symptoms usually begin within 1-3 d and include: anxiety, insomnia, irritability, mood lability, nausea/vomiting, dizziness, headache, dystonia, tremor, chills, fatigue, lethargy, and myalgia ("flu-like symptoms")
- treatment: symptoms may last between 1-3 wk, but can be relieved within 24 h by restarting antidepressant at the same dosage the patient was taking and initiating a slower taper over several weeks
- consider avoiding drugs with a short half-life



**Symptoms of Antidepressant Discontinuation**

**FINISH**
**F**lu-like symptoms
**I**nsomnia
**N**ausea
**I**mbalance
**S**ensory disturbances
**H**yperarousal (anxiety/agitation)

## Mood Stabilizers

### General Prescribing Information
- examples: lithium, divalproex, lamotrigine, carbamazepine
- used as first-line monotherapy or in conjunction with atypical antipsychotics for acute episodes of bipolar disorder - depression, mania – or for long-term stabilization
- vary in their ability to "treat" (reduce symptoms acutely) or "stabilize" (prevent relapse and recurrence) manic and depressive symptoms; multi-agent therapy can be avoided in many patients but it is common
- before initiating, get baseline: CBC with diff and platelets, ECG (if patient >45 yr old or cardiovascular risk), BUN, Cr, electrolytes, TSH
- Also: screen for pregnancy, thyroid disease, neurological, renal, liver, cardiovascular diseases
- full effects may take 2-4 wk, thus may need acute coverage with benzodiazepines or antipsychotics

### Specific Prescribing Information
- detailed pharmacological guidelines available online from the Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD)
- for clinical information for treating bipolar disorder (see *Mood Disorders*, PS10)

**Table 21. Commonly Used Mood Stabilizers**

| | Lithium | Lamotrigine (Lamictal®) | Divalproex (Epival®) | Carbamazepine (Tegretol®) |
|---|---|---|---|---|
| **Indications** | **1st line**<br>Acute mania (monotherapy or with adjunct SGA)<br>Bipolar I depression (monotherapy or in combination with divalproex, SSRI, or bupropion)<br>Bipolar disorder maintenance (monotherapy or with adjunct SGA)<br><br>**Other uses**<br>Bipolar II depression<br>Augmentation of antidepressants in MDD and OCD<br>Schizoaffective disorder<br>Chronic aggression, antisocial behaviour<br>Recurrent depression | **1st line**<br>Bipolar I depression (monotherapy)<br>Bipolar disorder maintenance (limited efficacy in preventing mania, more effective when combined with lithium)<br><br>**Other uses**<br>Bipolar II depression<br><br>Not recommended for acute mania as monotherapy | **1st line**<br>Acute mania (monotherapy or with adjunct SGA)<br>Bipolar I depression (combination with lithium or SSRI)<br>Bipolar disorder maintenance (monotherapy or with adjunct SGA)<br><br>**Other uses**<br>Bipolar II depression<br>Rapid cycling bipolar disorder<br>Mixed phase/dysphoric mania | **2nd line**<br>Acute mania (monotherapy)<br>Bipolar disorder maintenance (monotherapy or in combination with lithium)<br><br>**Other uses**<br>Rapid cycling bipolar disorder |
| **Mode of Action** | Unknown<br>Therapeutic response within 7-14 d | May inhibit 5-HT3 receptors<br>May potentiate DA activity | Depresses synaptic transmission<br>Raises seizure threshold | Depresses synaptic transmission<br>Raises seizure threshold |
| **Dosage** | Adult: 600-1500 mg/d<br>Geriatric: 150-600 mg/d<br>Usually daily dosing | Note: very slow titration required due to risk of Stevens-Johnson Syndrome<br>Dose adjusted in patients taking other anticonvulsants<br>Daily dose: 100-200 mg/d | 750-2500 mg/d<br>Usually daily dosing with ER preparation | 400-1600 mg/d<br>Usually bid or tid dosing |
| **Therapeutic Level** | Adult: 0.8-1.0 mmol/L (1.0-1.25 mmol/L for acute mania)<br>Geriatric: 0.6-0.8 mmol/L | Therapeutic plasma level not established<br>Dosing based on therapeutic response | 17-50 mmol/L<br>Same therapeutic levels as used for seizure prophylaxis | 350-700 µmol/L<br>Same therapeutic levels as used for seizure prophylaxis |
| **Monitoring** | Monitor serum levels every 5-7 d until therapeutic (always wait 12 h after dose)<br>Then monitor monthly, then q2-3mo<br>Monitor thyroid function, creatinine q6mo, urinalysis q1yr | Monitor for skin rash and suicidality, when initiating treatment | Monitor serum levels every 5-7 d until therapeutic<br>LFTs weekly x 1 mo, then monthly, then q2-3mo due to risk of liver dysfunction<br>Watch for signs of liver dysfunction: nausea, edema, malaise<br>Check platelets and monitor levels to adjust dosage and confirm adherence | Monitor serum levels every 5-7 d until therapeutic<br>Weekly blood counts for 1st mo, due to risk of agranulocytosis<br>Watch for signs of blood dyscrasias: fever, rash, sore throat, easy bruising |
| **Side Effects** | GI: N/V, diarrhea, stomach pain<br>GU: polyuria, polydipsia, nephrogenic DI, GN, renal failure,<br>CNS: fine tremor, headache, fatigue, lethargy<br>Hematologic: reversible benign leukocytosis<br>Other: teratogenic (Ebstein's anomaly), hypothyroidism, weight gain, edema, psoriasis, muscle weakness, bradycardia, ECG changes | Skin: rash (consider discontinuing due to risk of Steven-Johnson syndrome), slow dose titration to reduce risk<br>Otherwise, usually well tolerated (GI: N/V, diarrhea<br>CNS: ataxia, dizziness, diplopia, headache, somnolence<br>Other: anxiety) | GI: liver dysfunction, N/V, diarrhea<br>CNS: ataxia, drowsiness, tremor, sedation, cognitive blurring<br>Other: hair loss, weight gain, thrombocytopenia, neural tube defects when used in pregnancy | GI: N/V, diarrhea, hepatic toxicity<br>CNS: ataxia, dizziness, slurred speech, drowsiness, confusion, nystagmus, diplopia<br>Hematologic: transient leukopenia (10%), rare agranulocytosis, aplastic anemia<br>Skin: rash (5% risk; consider discontinuing drug because of risk of Stevens-Johnson syndrome)<br>Other: neural tube defects when used in pregnancy |
| **Interactions** | NSAIDs, thiazides, ACE inhibitors, and metronidazole decrease clearance, risk for lithium toxicity | | OCP | OCP |

## Lithium Toxicity

- clinical diagnosis as toxicity can occur at therapeutic levels
- **common causes**: overdose, sodium/fluid loss, concurrent medical illness or initiation of NSAIDs or diuretics
- **clinical feature**
  - GI: severe nausea/vomiting and diarrhea
  - cerebellar: ataxia, slurred speech, lack of coordination
  - cerebral: drowsiness, myoclonus, tremor, upper motor neuron signs, seizures, delirium, coma
- **management**
  - discontinue lithium for several days and begin again at a lower dose when lithium level has fallen to a non-toxic range
  - monitor serum lithium levels, BUN, electrolytes
  - IV saline
  - hemodialysis if lithium >2 mmol/L, coma, shock, severe dehydration, failure to respond to treatment after 24 h, or deterioration



Long-term lithium use can lead to a nephropathy and diabetes insipidus in some patients

# Anxiolytics

- anxiolytics mask or alleviate symptoms
- **indications**
  - short-term treatment of anxiety disorders, insomnia, alcohol withdrawal (especially delirium tremens), barbiturate withdrawal, akathisia due to antipsychotics, seizure disorders, musculoskeletal disorders, agitation or aggression associated with acute mania, or psychosis (i.e. ED, ICU)
- **relative contraindications**
  - major depression (except as an adjunct to other treatment), history of drug/alcohol abuse, caution in pregnancy/breastfeeding
- **mechanism of action**
  - benzodiazepines: potentiate binding of GABA to its receptors; results in decreased neuronal activity
  - buspirone: partial agonist of 5-HT1A receptors

## Benzodiazepines

- should be used for limited periods (i.e. days-weeks) to avoid tolerance and dependence
- all benzodiazepines are sedating, decrease respiratory drive, and increase risk for falls, confusion, and MVAs; be wary with use in the elderly
- have similar efficacy, so choice depends on half-life, metabolites, and route or schedule of administration
- taper slowly over weeks-months because they can cause withdrawal reactions (see below)
- avoid alcohol because of potentiation of CNS depression; caution with drinking and driving/machinery use
- **side effects**
  - CNS: drowsiness, cognitive impairment, reduced motor coordination (falls), memory impairment
  - physical dependence, tolerance
- **withdrawal**
  - low dose withdrawal symptoms: tachycardia, HTN, panic, rebound insomnia, anxiety, impaired memory and concentration, perceptual disturbances
  - high dose or rapid withdrawal symptoms: hyperpyrexia, seizures, death
  - onset: 1-2 d (short-acting), 2-4 d (long-acting)
  - duration: days-weeks
  - complication with above 50 mg diazepam/day or abrupt withdrawal: autonomic hyperactivity, seizures, delirium, arrhythmias
  - management: taper slowly, may need to switch to a long-acting benzodiazepine
  - similar to but less severe than alcohol withdrawal; can be fatal
- **overdose**
  - overdose is common but rarely fatal unless combined with other substances
  - more dangerous or potentially fatal when combined with alcohol, other CNS depressants, opioids, or TCAs



**Benzodiazepine Antagonist – Flumazenil (Anexate®)**
- Use for suspected benzodiazepine overdose
- Specific antagonist at the benzodiazepine receptor site

## Buspirone (Buspar®)

- primary use: GAD
- may be preferred over benzodiazepines because it is non-sedating, has no interaction with alcohol, does not alter seizure threshold, not prone to abuse
- onset of action: 2 wk
- side effects: dizziness, drowsiness, nausea, headache, nervousness, EPS

**Table 22. Dosing and Indications for Common Anxiolytics**

| Class | Drug | Dose Range (mg/d) | $t_{1/2}$ (h) | Appropriate Use |
|---|---|---|---|---|
| **Benzodiazepines** | | | | |
| Long-acting | clonazepam (Rivotril®) | 0.25-4 | 18-50 | Seizure prevention, akathisia, generalized anxiety disorder, panic disorder |
| | diazepam (Valium®) | 2-40 | 30-100 | Seizure prevention, muscle relaxant, alcohol withdrawal, generalized anxiety |
| | chlordiazepoxide (Librium®) | 5-300 | 30-100 | Alcohol withdrawal |
| | flurazepam (Dalmane®) | 15-30 | 50-160 | Should be avoided |
| Short-acting | alprazolam (Xanax®) | 0.25-4.0 | 6-20 | Should be avoided due to high dependency rate |
| | lorazepam (Ativan®) | 0.5-6.0 | 10-20 | Alcohol withdrawal (no first-pass liver metabolism), akathisia, short-term sedation for anxiety during procedures (i.e. CT or MRI), generalized anxiety; sublingual or IM for rapid action |
| | oxazepam (Serax®) | 10-120 | 8-12 | Alcohol withdrawal (no first-pass liver metabolism), generalized anxiety disorder |
| | temazepam (Restoril®) | 7.5-30 | 8-20 | Should be avoided |
| | triazolam (Halcion®) | 0.125-0.5 | 1.5-5 | Shortest $t_{1/2}$, rapid sleep without daytime sedation (i.e. overnight plane travel), but risk of rebound insomnia |
| **Azapirones** | | | | |
| | zopiclone (Imovane®) | 5-7.5 | 3.8-6.5 | Sleep (confusion less likely than with benzodiazepines) |



**Benzodiazepines**

**LOT**
**L**orazepam
**O**xazepam
**T**emazepam
Safe for patients with impaired liver function because not metabolized by liver

# Somatic Therapies

## Electroconvulsive Therapy

- various methodological improvements have been made since the first treatment in 1938 to reduce adverse effects
- modern ECT: induction of a generalized seizure using an electrical pulse through scalp electrodes while the patient is under general anesthesia with a muscle relaxant
- considerations: unilateral vs. bilateral electrode placement, pulse rate, energy, number, and spacing of treatments
- usual course is 6-12 treatments, 2-3 treatments per wk
- **indications**
  - depression: poor response to antidepressant (unipolar, bipolar I, bipolar II), psychotic features, catatonic features, when medications may be unsafe or rapid response is needed (i.e. cachexia, severe dehydration, frail elderly, high suicide risk)
  - catatonia: refractory, severe, or life-threatening
  - schizophrenia: acute symptoms with poor response to antipsychotics, catatonia, history of NMS
  - mania: refractory, severe or life-threatening situation
  - personal or family history of good response to ECT
  - inconclusive evidence for OCD
- **adverse effects**: risk of anesthesia (equal to risk of ECT), memory loss (may be retrograde and/or anterograde, tends to resolve by 6-9 mo, permanent impairment controversial), headaches, myalgias
- unilateral ECT causes less memory loss than bilateral but may not be as effective
- **contraindications**: no absolute contraindications; relative contraindications: increased intracranial pressure, recent (<4 wk) hemorrhagic stroke, recent (<2 wk) MI, requires special monitoring

**ECT in Society**
Prior to the 1940's, ECT was performed without the use of muscle relaxants, resulting in seizures with full-scale convulsions and rare but serious complications such as vertebral and long-bone fractures. This practice may have led to negative societal perceptions of ECT, further perpetuated by negative depictions in popular culture. Despite ongoing stigmatization, ECT as it is practiced today is an effective and safe option for patients with severe mental illness

**Electroconvulsive Therapy for Treatment Resistant Schizophrenia**
Cochrane DB Syst Rev 2019:CD011847.
**Objectives**: Assess benefits and harms of ECT for people with treatment-resistant schizophrenia.
**Outcomes**: Moderate-quality evidence indicates that relative to standard care, ECT has a positive effect on medium-term clinical response for people with treatment-resistant schizophrenia. However, there is no clear and convincing advantage or disadvantage for adding ECT to standard care for other outcomes.

## Repetitive Transcranial Magnetic Stimulation (rTMS)

- noninvasive production of focal electrical currents in select brain circuits using magnetic induction
- indications: strong evidence for treatment-resistant depression, pain disorders; possibly efficacious for anxiety disorders, eating disorders, substance use disorders
- adverse effects: common – transient local discomfort, hearing issues, or cognitive changes; rare - seizure, syncope, mania induction

## Magnetic Seizure Therapy (Experimental)

- generalized seizure induction using strong magnetic current
- early studies demonstrate efficacy for depression as well as anxiety, with reduced memory effects vs. ECT

## Neurosurgical Treatments

### Ablative/Lesion Procedures
- used for MDD or OCD unresponsive to all other forms of treatment; efficacy ranges from 25-75% depending on procedure
- adverse effects: related to lesion location and size, high risk of suicide in those who are not helped by surgery

### Deep Brain Stimulation (Experimental)
- placement of small electrode leads in specific brain areas to alter neuronal signaling, usually for MDD unresponsive to all other forms of treatment
- response rates (>50% symptom reduction) of 40-70%, adverse effects related to surgical risks and poor treatment response

### Vagus Nerve Stimulation
- direct, intermittent electrical stimulation of left cervical vagus nerve via implanted pulse generator
- used for chronic, recurrent MDD with poor response to previous therapy and ECT; slow onset, approximately 30% response rate after 1 yr

## Other Therapy Modalities

### Phototherapy (Light Box Therapy)
- bright light source exposure (usually 10,000 lux) for 30-60 min; best if done daily in the morning
- proposed mechanisms: reverses pathological alterations in circadian rhythm through action on suprachiasmatic nucleus
- indications: seasonal affective disorder (SAD), non-seasonal depression (as augmentation), some sleep disorders
- adverse effects: mania induction, reaction with photosensitizing drug or photosensitive eye or skin conditions

### Aerobic Exercise

- moderate-intense aerobic exercise is associated with acute increased release of serotonin, phenethylamine, brain-derived neurotrophic factor, endogenous opioids, and cannabinoids (likely this combination is what contributes to the "runner's high")
- long term increases grey matter in multiple areas, as well as improvements in cognition, memory, and stress tolerance
- indications: monotherapy for mild-moderate MDD; adjunctive therapy for moderate-severe MDD; research suggests 30 min of supervised moderate-intensity exercise at least 3 times weekly for a minimum of 9 wk is as effective as psychotherapy or antidepressant medications
- may be helpful in PTSD, schizophrenia

# Canadian Legal Issues

## Common Forms

**Table 23. Common Forms Under the Mental Health Act (in Ontario)**

| Form | Who Signs | When | Expiration Date | Right of Patient to Review Board Hearing | Options Before Form Expires |
|---|---|---|---|---|---|
| **Form 1:** Application by physician to hospitalize a patient for psychiatric assessment against his/her will in a schedule 1 facility (Form 42 given to patient) | Any MD | Within 7 d after having examined the patient | 72 h after hospitalization<br>Void if not implemented within 7 d | No | Form 3 and 30 or voluntary admission or send home ± follow-up |
| **Form 2:** Order by Justice of the Peace to bring patient to a hospital for a psychiatric assessment against his/her will | Justice of the Peace | No statutory time restriction | 7 d from when completed<br>Purpose of form is complete once patient brought to hospital | No | Form 1 and 42 or send home ± follow-up |
| **Form 3:** Certificate of involuntary admission to a schedule 1 facility (Form 30 given to patient, notice to rights advisor) | Any MD other than MD who completed Form 1 | Before expiration of Form 1<br>Any time to change status of a voluntary inpatient | 14 d | Yes | Form 4 and 30 or Voluntary admission (Form 5) |
| **Form 4:** Certificate of renewal of involuntary admission to a schedule 1 facility (original Form 30 given to patient, notice to rights advisor) | Attending MD following patient on Form 3 | Prior to expiration of Form 3 | First: 1 mo<br>Second: 2 mo<br>Third: 3 mo (max) | Yes | Form 4 and 30 or Voluntary admission (Form 5) |
| **Form 5:** Change to informal/voluntary status | Attending MD following patient on Form 3/4 | Whenever deemed appropriate | N/A | N/A | N/A |
| **Form 30:** Notice to patient that they are now under involuntary admission on either Form 3 or 4. Original to the patient, copy to chart | Attending MD | Whenever Form 3 or Form 4 filled | N/A | Yes | N/A |
| **Form 33:** Notice to patient that patient is incapable of consenting to treatment, and/or management of property and/or disclosure of health information (original copy to patient) | Attending MD | Whenever deemed appropriate | N/A | Yes | N/A |

* Schedule 1 Facilities: Able to provide intensive inpatient and outpatient care

**Form 1: Application for Psychiatric Assessment**

- Filled out when patients are thought to be in imminent danger to harm themselves (suicide) or others (homicide) or when they are incapable of self-care (i.e. not dressed for freezing weather) and are suffering from an apparent mental disorder
- Based on any combination of the physician's own observations and facts communicated by others
- Box A or Box B completed
- **Box A**: Serious Harm Test
- The Past/Present Test assesses current behaviours/threats/attempts
- The Future Test assesses the likelihood of serious harm occurring as a result of the presenting mental disorder. In this section, one should document evidence of the mental disorder and concerning behaviour/thoughts
- **Box B**: Patients with a known mental disorder, who are incapable of consenting to treatment (substitute decision-maker needed), have previously received treatment and improved, and are currently at risk of serious harm due to the same mental disorder

## Consent

- see Ethical, Legal, and Organizational Medicine, ELOM7

# Community Treatment Order (CTO)

- purpose: a CTO orders a person suffering from a serious mental disorder to receive treatment and supervision in the community. Based on a comprehensive plan outlining medications, appointments, and other care believed necessary to allow the person to live in the community (vs. in a psychiatric facility, where conditions are more restrictive)
- intended for those who:
  - due to their serious mental disorder, experience a pattern of admission to a psychiatric facility where condition is usually stabilized
  - after being released, these patients often lack supervision and stop treatment, leading to destabilization
  - due to the destabilization of their condition, these patients usually require re-admission to hospital
  - if CTO violated (i.e. treatment not taken), patient brought in by police to hospital for treatment as per CTO
- criteria for a physician to issue a CTO
  - patient with a prior history of hospitalization
  - a community treatment plan for the person has been made
  - examination by a physician within the previous 72 h before entering into the CTO plan
  - ability of the person subject to the CTO to comply with it
  - consultation with a rights advisor and consent of the person or the person's substitute decision maker
- CTOs are valid for 6 mo unless they are renewed or terminated at an earlier date such as
  - where the person fails to comply with the CTO
  - when the person or his/her substitute decision-maker withdraws consent to the community treatment plan
- CTO process is consent-based and all statutory protections governing informed consent apply
- the rights of a person subject to a CTO include
  - the right to a review by the Consent and Capacity Board with appeal to the courts each time a CTO is issued or renewed
  - a mandatory review by the Consent and Capacity Board every second time a CTO is renewed
  - the right to request a re-examination by the issuing physician to determine if the CTO is still necessary for the person to live in the community
  - the right to review findings of incapacity to consent to treatment
  - provisions for rights advice



**CTO Legislature**
- Ontario passed CTO legislature on December 1, 2000 (known as "Brian's Law")
- Similar CTOs have been implemented in Saskatchewan (1995), Manitoba (1997), and British Columbia (1999)

# Duty to Inform/Warn

- see Ethical, Legal, and Organizational Medicine, ELOM6

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# PH Public Health and Preventive Medicine

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For more detail on topics covered in this chapter, use website http://phprimer.afmc.ca/ as a resource

# Acronyms

| | |
|---|---|
| ADLs | activities of daily living |
| AR | attributable risk |
| BMI | body mass index |
| CAS | Children's Aid Society |
| CBA | cost benefit analysis |
| CEA | cost effectiveness analysis |
| CFR | case fatality rate |
| CPH | Chief Public Health Officer |
| CTFPHC | Canadian Task Force on Preventive Health Care |
| DALY | disability adjusted life years |
| DDT | dichlorodiphenyltrichloroethane |
| DM | diabetes mellitus |
| EBM | evidence-based medicine |
| ECs | electronic cigarettes |
| ESL | English as a second language |
| HC | Health Canada |
| FP | false positives |
| FN | false negatives |
| FOBT | fecal occult blood |
| GRADE | grading of recommendations assessment, development and evaluation |
| IMR | infant mortality ratio |
| ITT | intention to treat analysis |
| LICO | low income cut-off |
| LR | likelihood ratio |
| MH | Medical Health Officer |
| MOH | Medical Officer of Health |
| MMR | maternal mortality ratio |
| MSDS | Material Safety Data Sheets |
| NNH | number needed to harm |
| NNT | number needed to treat |
| NPV | negative predictive value |
| OR | odds ratio |
| PFT | pulmonary function test |
| PHAC | Public Health Agency of Canada |
| PP | per protocol analysis |
| PPV | positive predictive value |
| PSA | prostate screening antigen |
| PYLL | potential years of life lost |
| QALY | quality adjusted life years |
| QI | quality improvement |
| RCT | randomized controlled trial |
| RR | relative risk |
| SARS | severe acute respiratory syndrome |
| SMR | standardized mortality ratio |
| SN | sensitivity |
| SP | specificity |
| TP | true positives |
| TN | true negatives |
| WHMIS | Workplace Hazardous Materials Information System |
| WHO | World Health Organization |
| WSIB | Workplace Safety and Insurance Board |

# Public Health Context

- see Ethical, Legal, and Organizational Medicine, ELOM2 *Overview of Canadian Healthcare System* for the organization of health care in Canada including the legal foundation and historical context

### Definitions

- **population health**
  - refers to the health of defined groups of people, their health determinants, trends in health, and health inequalities
  - influenced by: physical, biological, social, environmental, and economic factors; personal health behaviours; health care services
  - broader scope compared to public health; accounts for socioeconomic, policy, historical issues
- **public health**
  - an organized activity of society to promote, protect, improve, and when necessary, restore the health of individuals, specified groups, or the entire population
  - a combination of sciences, skills, and values that function through collective societal activities and involve programs, services, and institutions aimed at protecting and improving the health of all people
  - public health services in many provinces (e.g. Ontario) are administered, funded and delivered entirely separately from health care services
- **epidemiology**
  - "study of the distribution […] of determinants of disease, health-related states, and events in populations"
- **public health and preventive medicine** (formerly called community medicine)
  - the medical specialty that focuses on population rather than individuals' health through health protection and illness and injury prevention
  - works with diverse populations to address social determinants of health and promotes health equity
  - 5 year Royal College training in medical skills and knowledge, epidemiology, statistics, social sciences, public administration, policy development, program management, and leadership

Sources: Shah, CP. Chapter 2 Measurement and Investigation. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003
Shah, CP. Chapter 15 Community Health Services. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003

**Preparing for the LMCC**
The AFMC Primer on Population Health is the core text for the LMCC and is available as an online resource on the AFMC website (http://phprimer.afmc.ca)
For the LMCC exam, it is recommended that you also read Chapter 15 in Shah CP. Public health and preventive medicine in Canada, 5th ed. Toronto: Elsevier, 2003

**Historical Perspective**
Over the last century, Public Health has evolved through three main epidemiological phases:
- Infectious diseases: controlled in the more developed countries but an issue in less developed countries (e.g. polio, malaria)
- Chronic diseases: have increased morbidity and mortality (e.g. heart disease and cancer due to risk factors and/or exposures)
- Re-emerging infectious diseases: emerge due to unfamiliar or new pathogens, inefficient or inappropriate antibiotic use, travel, and global warming (e.g. HIV, drug resistant TB, and malaria)

# Public Health in Canada

The Public Health System in Canada is composed of various agencies at the Federal (Public Health Agency of Canada), Provincial (Public Health Ontario) and Municipal/Local levels (local public health units). The organization of the public health system in each province varies widely and is usually separate from the health care system.

**Mission of the Public Health Agency of Canada (federal only):** to promote and protect the health of Canadians through leadership, partnership, innovation, and action in public health

- local public health units and services within regional health authorities (in most provinces except Ontario, where local public health units are either autonomous or within local government) provide programs and activities for health protection, promotion, and disease prevention at local and regional levels
- catchment-area populations range widely (100s-1,000,000s), covering areas of 15 $km^2$ to 1.5 million $km^2$
- the "core functions" of public health include six essential activities

(The Organization of Health Services in Canada. AFMC Primer on Population Health, Accessed: March 25 2016)

1. **health protection**: measures taken to address potential risks to health at the population level through regulation and advising government (e.g. safe water and food supply)
2. **health surveillance**: monitoring and predicting health outcomes and determinants with systematic, longitudinal data collection
3. **disease and injury prevention**: address infectious disease through preventive (e.g. vaccination, droplet protection) and control (e.g. quarantine) measures; reduce morbidity through lifestyle improvement
4. **population health assessment**: studying and engaging with a community to understand their needs and improve policies and services

**Chief Public Health Officer (CPHO) of Canada**
- Responsible for the Public Health Agency of Canada (PHAC) and reports to the Minister of Health
- As the federal government's lead public health professional, provides advice to the Minister of Health and Government of Canada and collaborates with other governments, jurisdictions, agencies, organizations, and countries on health matters
- Communicates public health information to health professionals, stakeholders, and the public
- In an emergency, such as an outbreak or natural disaster, directs PHAC staff, including medical professionals, scientists, and epidemiologists, to coordinate emergency response

Source: Public Health Agency of Canada. http://www.phac-aspc.gc.ca/cpho-acsp/cpho-acsp-role-eng.ph

5. **health promotion**: advocate for improved health through broad community and government measures (e.g. policy, interventions, community organizations)
6. **emergency preparedness and response**: developing protocols and infrastructure for natural (e.g. hurricane) and man-made (e.g. opioid crisis) disasters. In many types of health-related disasters, public health leads the disaster response

Sources: Shah, CP. Chapter 15 Community Health Services. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003
The Association of Faculties of Medicine of Canada Public Health Educators' Network. The Organization of Health Services in Canada. AFMC Primer on Population Health

# Legislation and Public Health in Canada

**Table 1. Legislation and Public Health in Canada**

| Federal | Provincial | Municipal (Ontario) |
|---|---|---|
| **Health Canada**<br>• Provides health services to Indigenous peoples, the Canadian military, and veterans<br>• Approves new drugs and medical devices<br>• Food Guide<br>**Public Health Agency of Canada** (main Government of Canada agency responsible for public health)<br>• An independent body created post-SARS to strengthen public health capacity and response<br>• Focuses on preventing chronic diseases, preventing injuries, and responding to public health emergencies and infectious disease outbreaks<br>• Activities include CTFPHC guideline secretariat, knowledge brokers<br>• Oversees immigration screening, protects Canadian borders (e.g. airport health inspection)<br>• Liaises with the World Health Organization (WHO) on global health issues<br>**Canadian Food Inspection Agency**<br>• Regulates food labeling<br>• Deals with animal-related infections<br>**Canadian Institutes of Health Research (CIHR)**<br>• Formed in 2000 to support research to improve health and the healthcare system | Each province has its own Public Health Act or equivalent (e.g. the *Health Protection and Promotion Act* in Ontario) and agencies (e.g. Public Health Ontario)<br>• Designates the creation of geographic areas for the provision of public health services<br>• Gives powers to the Chief Medical Officer of Health to control public health hazards<br>• Specifies diseases to be reported to public health units by physicians, laboratories, and hospitals (see *Appendix*, PH26)<br>• Mandate programs that address public health issues, environmental health, and chronic disease prevention | Local public health units (e.g. Middlesex-London Health Unit) deliver programs mandated by provincial, municipal or regional legislation and are responsible for the delivery of most public health services, such as:<br>• Infectious disease control, including the follow-up of reported diseases and management of local outbreaks<br>• Inspection of food premises including those in hospitals, nursing homes, and restaurants<br>• Family health services including pre-conception, preschool, school-aged, and adult health programs<br>• Tobacco control legislation enforcement<br>• Assessment and management of local environmental health risks<br>• Collection and dissemination of local health status reports<br>• Oral health<br>• By-laws may be approved by municipal governments to facilitate public health issues |



**Example of a Municipal Health Unit: The Middlesex-London Health Unit**
- Serves 450,000 people living, working, visiting, and studying in the city of London and Middlesex county
- 275 full-time staff including medical officers of health (physicians), public health nurses, epidemiologists, health promotion educators, dental hygiene managers, etc.
- Services include infectious disease control, ensuring environmental health standards, health promotion, and providing family health programs



**Medical Officer of Health (MOH) (Ontario)**
- May be called "Medical Health Officer" (MHO) in other provinces
- Appointed to each public health unit by the board of health
- Held by a Public Health and Preventive Medicine specialist physician
- Responsibilities include oversight of a multidisciplinary team who:
  - Collect and analyze epidemiological data
  - Provide occupational and environmental health surveillance
  - Implement health programs, including tobacco use prevention inspections (restaurants, doctor's offices, tattoo parlors) and prenatal courses
  - The Medical Officer of Health, by law, can require an individual/premise/agency or a person to take or refrain from any action due to a public health hazard. (Section 13 and 22 of the HPPA)

# Determinants of Health

## Concepts of Health

- **wellness**: "state of dynamic physical, mental, social, and spiritual well-being that enables a person to achieve full potential and have an enjoyable life"
- **disease**: "abnormal, medically-defined changes in the structure or function of the human body"
- **illness**: "an individual's experience or subjective perception of a lack of physical or mental well-being and consequent inability to function normally in social roles"
- **illness behaviour**: an individual's actions resulting from and responding to their illness, including their interactions or avoidance of the health care system
- **sickness**: views the individual and their society hold towards a health condition, affecting their thoughts and actions
- **impairment**: "any loss or abnormality of psychological, physiological, or anatomical structure or function"
- **disability**: "any restriction or lack of ability to perform an activity within the range considered normal for a human being"
- **handicap**: a disadvantage for an individual arising from impairment or disability
  - "limits or prevents the fulfillment of an individual's normal role as determined by society and depends on age, sex, social, and cultural factors"
- **health equity**: when all people have "the opportunity to attain their full health potential" and no one is "disadvantaged from achieving this potential because of their social position or other socially determined circumstance." Health inequities are systematic differences in the health of individuals/groups which are considered unjust
- **health equality**: defined as where populations have equal or similar health status. Health inequalities are systematic differences in the health of groups that do not necessarily carry a moral judgement



**Definitions of Health**
- First multidimensional definition of health, as defined by the WHO in 1948: "state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"
- WHO updated the definition (socio-ecological definition) of health in 1986: "The ability to identify and to realize aspirations, to satisfy needs, and to change or cope with the environment. Health is therefore a resource for everyday life, not the objective of living. Health is a positive concept emphasizing social and personal resources, as well as physical capacities" (Ottawa Charter for Health Promotion)
- Other definitions of health have since been proposed that incorporate other dimensions of health (e.g. "Health is a social, economic, and political issue and above all a fundamental human right" – The People's Charter for Health)

## Determinants of Health

- 1974: the Honourable Marc Lalonde, federal Minister of Health, publishes *A New Perspective on the Health of Canadians* which outlines four factors that determine health: "human biology, environment, lifestyle, and health care organizations." The idea of determinants of health has since been expanded and refined to include many additional factors

Sources: Shah, CP. Concepts, Determinants, and Promotion of Health. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003
The Association of Faculties of Medicine of Canada Public Health Educators' Network. Concepts of Health and Illness. AFMC Primer on Population Health

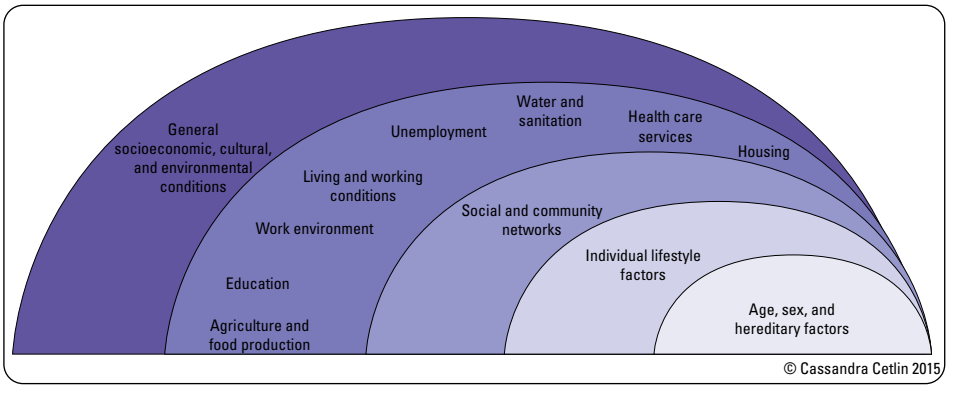



**Figure 1. Population health model**
Adapted from Dahlgreen G, Whitehead M. European strategies for tackling social inequities in health: Leveling up Part 2. World Health Organization, 2006

**Determinants of Health**
- Income and social status
- Social support networks
- Education and literacy
- Employment and working conditions
- Social and work environments
- Physical environment
- Personal health practices and coping skills
- Healthy child development
- Biology, genetics, and epigenetics
- Health services
- Gender
- Culture
- Racism

Source: Public Health Agency of Canada www.phac-aspc.gc.ca/ph-sp/determinants/determinants-eng.php

**Ottawa Charter for Health Promotion (1986)**
- Health promotion: the process of enabling people to increase control over and improve their health
- The charter states that governments and health care providers should be involved in a health promotion process that includes:
  1. Building healthy public policy
  2. Creating supportive environments
  3. Strengthening community action
  4. Developing personal skills
  5. Re-orienting health services

- **cultural safety**: "interactions with people from different cultures that treat them respectfully in a manner that acknowledges relevant differences but does not create a sense of discrimination"
- **cultural sensitivity**: "being aware of (and understanding) the characteristic values and perceptions of your own culture and the way in which this may shape your approach to patients from other cultures"

# Vulnerable Populations

**Table 2. Health Determinants of Vulnerable Populations**

| | Definition | Physical | Environment | Personal Risk Factors | Population-Specific Interventions |
|---|---|---|---|---|---|
| **Indigenous Peoples** | Four specific groups: First Nations Status Indians (registered under the *Indian Act*), non-status Indians, Métis, and Inuit | Colonization<br>Systemic racism<br>Low income<br>Family violence<br>Low education status<br>Unemployment<br>Homelessness<br>Longer length of disability | Crowded housing<br>Inefficient ventilation<br>Environmental toxins (botulism)<br>TB declining but prevalence higher than rest of population | Smoking<br>Substance misuse<br>Gambling<br>Poor nutrition<br>Sedentary lifestyle<br>High BMI<br>Higher risk of suicide | Mental health awareness<br>Indigenous-specific DM initiatives<br>Substance abuse treatment programs<br>Cultural continuity |
| **Black Population** | Sub-Saharan African Ancestry, diverse cultures and histories but socially classified as 'Black'<br>3rd largest "visible minority" group in Canada<br>43% Canadian-born | Systemic racism<br>Low income<br><br>The Nova Scotian Black population has been in Canada for centuries; historically displaced into rural settings<br>Newer immigrants tend to live in urban centres | Variable, depending on socioeconomic status and immigrant status/ history in Canada | High BMI<br>Higher risk DM and hypertension<br><br>(poor data quality for identifying disparities in Canada due to lack of collection of race-based data) | Culturally-specific and safe practices<br><br>Anti-Racist approaches to care, policy, programming |
| **Isolated Seniors** | Individuals >65 yr | Elder abuse<br>Lack of emotional support<br>Isolation | Low hazard tolerance<br>Institutionalization<br>Mobility issues | Inactivity<br>Polypharmacy<br>Medical comorbidities | Aging in place of choice<br>Falls and injury prevention<br>Mental health promotion<br>Preventing abuse and neglect |

**Ottawa Charter for Health Promotion (1986)**
- Health promotion: the process of enabling people to increase control over and improve their health
- Some health promotion can be achieved through clinical interactions with patients, but most health promotion is done at the population level by public health professionals and agencies by engaging stakeholders, formilating policy and influencing in upstream factors, the Ottawa Charter is a framework for thinking about health promotion
- The Ottawa charter states that governments and health care providers should be involved in a health promotion process that includes:
  1. Building healthy public policy
  2. Creating supportive environments
  3. Strengthening community action
  4. Developing personal skills
  5. Re-orienting health services

**Table 2. Health Determinants of Vulnerable Populations** (continued)

| | Definition | Physical | Environment | Personal Risk Factors | Population-Specific Interventions |
|---|---|---|---|---|---|
| **Children in Poverty** | Based on Low Income Cut Offs (LICO)<br>LICO is an income threshold below which a family will likely devote a larger share of its income on the necessities of food, shelter, and clothing than the average family | Low income<br>Family dysfunction<br>Lack of educational opportunities | Housing availability<br>Unsafe housing<br>Lack of recreational space | Poor supervision<br>Food insecurity<br>High risk behaviours | Improvements in family income most significant<br>Early childhood education |
| **People with Disabilities** | Includes impairments, activity limitations, and participation restrictions | Low income<br>Low education status<br>Discrimination<br>Stigma | Institutionalization<br>Barriers to access<br>Transportation challenges | Substance misuse<br>Poor nutrition<br>Inactivity<br>Dependency for ADLs | Transportation support<br>Multidisciplinary care<br>Unique support for individuals with specific disabilities (e.g. Trisomy 21) |
| **New Immigrants** | Person born outside of Canada who has been granted the right to live in Canada permanently by immigration authorities | Access to community services<br>Cultural perspectives (including reliance on alternative health practices) | Exposure to diseases and conditions in country of origin (e.g. smoke from wood fires, incidence of TB, etc.) | Employment ESL<br>Healthy Newcomer Effect (health worsens over time to match that of the general population)<br>Cultural or religious expectations | Women's health<br>Mental health<br>Infectious diseases (syphilis blood test, CXR, HIV)<br>Dental and vision screening<br>Vaccinations<br>Cancer screening |
| **Homeless Persons** | An individual who lacks permanent housing | Low income<br>Food insecurity<br>Mental illness | Exposure to temperature extremes<br>Infections such as West Nile Virus | Substance misuse<br>Violence | Safe housing<br>Addictions support<br>Mental health |
| **Refugee Health** | Forced to flee country of origin because of a well-founded fear of persecution and given protection by the Government of Canada<br><br>Refugee claimant: Arrive in Canada and ask to be considered refugee | Post-traumatic stress disorders<br>Depression<br>Adjustment problems<br><br>Partial health coverage via Interim Federal Health Program | Diseases and conditions in country of origin (e.g. malaria, TB, onchocerciasis, etc.)<br>Direct and indirect effects of war | Employment<br>ESL<br>Longstanding prior lack of access to health care (chronically neglected problems)<br>Cultural or religious expectations | Vaccinations<br>Women's health<br>Mental health<br>Infectious diseases<br>Dental and vision screening<br>Political advocacy |

Note: this chart delineates the major challenges faced by each group, but the issues listed are not unique to each population.
Sources: Shah, CP. The Health of Vulnerable Groups. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003.



**New Immigrants to Canada**

- Mandatory medical exams on entry to Canada by a designated medical practitioner
- Complete medical examination for all persons of all ages
- Chest x-ray and report for persons ≥11 yr
- Urinalysis for persons ≥5 yr
- Syphilis serology for persons ≥15 yr
- HIV testing for applicants ≥15 yr, as well as for those children who have received blood or blood products, have a known HIV-positive mother, or have an identified risk. An ELISA HIV screening test should be done for HIV 1 and HIV 2
- Serum creatinine if the applicant has hypertension (resting blood pressure greater than 140/90 mmHg), a history of treated hypertension, DM, autoimmune disorder, persistent proteinuria, or kidney disorder

Citizenship and Immigration Canada Handbook
http://www.cic.gc.ca/english/resources/publications/dmp-handbook/

# Indigenous Health in Canada

## Definitions

- Indigenous peoples represent approximately 4.9% of the total population of Canada in 2016 and speak over 70 Indigenous languages
- 3 broad categories: First Nations (status and non-status), Metis, and Inuit
  - First Nations: includes over 600 diverse communities in Canada; status vs. non-status refers to the registration of First Nations peoples under the *Indian Act* (1876), which was originally established by the government to remove self-governing, residential, and traditional practice rights
  - Metis: descendants of the First Nations and European settlers; nearly 2/3 residing in cities, greatest percentage in Ontario
  - Inuit: roughly 75% of this population of 70,000 resides in the 4 Canadian Regions known as Inuit Nunangat, the Inuit Homeland. These include: Nunavut, Nunavik (N. Quebec) and Nunatsiavut (Labrador), and Inuvialuit (Northwest Territories)

## Young and Growing Populations

- between 2006-2016 the Indigenous populations have increased by 42.5%, 4x that of non-Indigenous Canadian population growth
- 32.1 is the average age of the Indigenous population, about 8 years younger than the non-Indigenous Canadian population
- but the aging Indigenous population is also growing, with anticipated doubling of >65 age group by 2036

## The Impact of Colonialism

- **colonialism**: subjugation of Indigenous peoples by the Europeans, leading to the loss of lands, cultural practices, and self-government
- **residential schools (1870s-1996):** placement of children from Indigenous groups in church-run, government-funded schools for the purpose of assimilation, resulting in loss of identity, alienation, and abuse, with long-lasting consequences of higher rates of addictions, abusive relationships, and suicide

- **Truth and Reconciliation Commission (2015):** mandated document created by the Canadian government and residential school survivors that preserves in writing the truth of residential schools and delineates recommendations for reconciliation. Many TRC recommendations pertain directly to health and healthcare providers
- **treaties and land claims:** inadequate services for those living on reserves leading to poverty and poor quality infrastructure, reflected in disproportionate burden of infectious diseases (e.g. pertussis, chlamydia, hepatitis, shigellosis)

### Traditional Approaches to Healing

- restoring balance in the four realms of spiritual, emotional, mental, and physical health of a person acting as an individual, as well as a member of a family, community, and nation
  - ideas represented by medicine wheel of First Nations peoples, the Learning Blanket of Inuit peoples, and the Metis tree model of Holistic Lifelong Learning
  - contrast to Western medicine focus of treating illness, leading to challenges for practitioners of Western medicine to meet Indigenous patients' needs
  - National Indigenous Health Organization (NIHO) offers 8 guidelines on practicing culturally safe health care for Indigenous patients including the need to allow Indigenous patients to access ceremony, song, and prayer; the need for information and for family support; guidelines for the appropriate disposal of body parts and for handling death

# Disease Prevention

### Natural History of Disease

- course of a disease from onset to resolution
  1. pathological onset
  2. presymptomatic stage: from onset to first appearance of symptoms/signs
  3. clinical manifestation of disease: may regress spontaneously, be subject to remissions and relapses, or progress to death

### Surveillance

- the continuous, systematic collection, analysis and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practice

Sources: World Health Organization. Public Health Surveillance. Accessed from: https://www.who.int/topics/public_health_surveillance/en/. 2019.

- **Types of Surveillance**
  - **passive surveillance**: reporting of disease data by all institutions that see patients, relying solely on the cooperation of health-care providers (laboratories, hospitals, health facilities, and private practitioners)
    - most common, least expensive, but difficult to ensure completeness and timeliness of data
  - **active surveillance**: regular visits to health facilities for reviewing medical records to identify suspected cases of disease under surveillance
    - resource-intensive, used when a disease is targeted for eradication where every possible case must be investigated, or for outbreak investigations
  - **sentinel surveillance**: selective reporting of disease data from a limited network of carefully selected reporting sites with a high probability of seeing cases in question,
    - well-designed system can be used to signal trends, identify outbreaks, and monitor the burden of disease in a community in a timely and cost-effective manner compared to other kinds of surveillance, although may be not as effective in identifying rare diseases, or diseases that occur outside the catchment area of sentinel sites

Sources: World Health Organization. Public Health Surveillance. Accessed from: https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/en/; https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/active/en/; https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/sentinel/en/

### Disease Prevention Strategies

- measures aimed at preventing the occurrence, interrupting through early detection and treatment, or slowing the progression of disease/mitigating the sequelae

**Table 3. Levels of Disease Prevention**

| Level of Prevention | Goal | Examples |
|---|---|---|
| **Primordial** | Preventing the development of risk factors | Education that begins in childhood about behaviour that can harm health<br>Programs that encourage physical activity |
| **Primary** | Protect health and prevent disease onset<br>Reducing exposure to risk factors | Immunization programs (e.g. measles, diphtheria, pertussis, tetanus, polio, see Pediatrics, P4)<br>Smoking cessation<br>Seatbelt use |
| **Secondary** | Early detection of (subclinical) disease to minimize morbidity and mortality | Mammography<br>Routine Pap smears |
| **Tertiary** | Treatment and rehabilitation of disease to prevent progression, permanent disability, and future disease | DM monitoring with HbA1c, eye exams, foot exams<br>Medication |

Basic Concepts in Prevention, Surveillance, and Health Promotion. AFMC Primer on Population Health (http://phprimer.afmc.ca/Part1-TheoryThinkingAboutHealthChapter4BasicConceptsInPreventionSurveillanceAndHealthPromotion/Thestagesofprevention)

**Passive Prevention**
Measures that operate without the person's active involvement (e.g. airbags in cars) are more effective than active prevention, measures that a person must do on their own (e.g. wearing a seatbelt)

**Example of Primary Prevention**
**HPV 9-Valent Vaccine and Its Efficacy in the Prevention of Cervical Cancer**
This is a nonavalent HPV vaccine covering strains 6, 11, 16, 18, 31, 33, 45, 52, and 58. The efficacy of this vaccine was studied in 4 randomized, double-blind, placebo-controlled trials on females between 11 and 26 yr of age and was found to prevent nearly 100% of precancerous cervical changes for up to 4 yr after vaccination

**Does Evidence Support Supervised Injection Sites?**
Can Fam Physician 2017 Nov;63(11):866
**Clinical question**: Do supervised injection sites (SISs) reduce mortality, hospitalizations, ambulance calls, or disease transmission?
**Bottom line**: Best evidence from cohort and modelling studies suggests that SISs are associated with lower overdose mortality (88 fewer overdose deaths per 100,000 person-years [PYs]), 67% fewer ambulance calls for treating overdoses, and a decrease in HIV infections. Effects on hospitalizations are unknown

## Screening (Secondary Prevention)

- "screening is a strategy used in a population to identify the possible presence of an as-yet-undiagnosed disease in individuals without signs or symptoms"
  - screening vs. case finding: screening tests are not diagnostic tests
  - the primary purpose of screening tests is to detect early disease or risk factors for disease in large numbers of apparently healthy individuals. The purpose of a diagnostic test is to establish the presence (or absence) of disease as a basis for treatment decisions in symptomatic or screen positive individuals (confirmatory test). Both screening and case finding seek to risk stratify for further investigation
  - to minimize biases and harms, and maximize benefits, screening is best done at the population level, not the individual clinical level, as part of a screening program (e.g. Provincial breast cancer screening program vs. screening by primary care/family physicians)
- **types of screening**
  - **universal screening**: screening all members of a population for a disease (e.g. phenylketonuria (PKU) and hypothyroidism in all newborns)
  - **selective screening**: screening of targeted subgroups of the population at risk for a disease (e.g. mammography in women >50 yr old)
  - **multiphasic screening**: the use of many measurements and investigations to look for many disease entities (e.g. periodic health exam)
- **types of bias in screening**
  - **lead-time bias**: overestimation of survival time 'from diagnosis' when the estimate is made from the time of screening, instead of the later time when the disease would have been diagnosed without screening
  - **length-time bias**: overestimation of the survival time due to screening at one time point including more stable cases than aggressive cases of disease, who may have shorter survival times

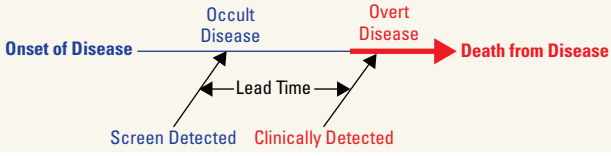



**Figure 2. Lead-time bias**

### Table 4. Ideal Criteria for Screening Tests

| Disease | Test | Health Care System |
|---|---|---|
| Causes significant suffering and/or death<br>Natural history must be understood<br>Must have an asymptomatic stage that can be detected by a test<br>Early detection and intervention must result in improved outcomes | High sensitivity<br>Safe, rapid, easy, relatively inexpensive<br>Acceptable to providers and the population<br>Continuously utilized | Adequate capacity for reporting, follow-up, and treatment of positive screens<br>Cost effective<br>Sustainable program<br>Clear policy guidelines on who to treat |

Adapted from: Shah CP. Public Health and Preventive Medicine in Canada, 5th ed. Toronto: Elsevier, 2003

## Health Promotion Strategies

### Table 5. Disease Prevention vs. Health Promotion Approach

| Disease Prevention | Health Promotion |
|---|---|
| Health = absence of disease | Health = positive and multidimensional concept |
| Medical model (passive role) | Participatory model of health |
| Aimed mainly at high-risk groups in the population | Aimed at the population in its total environment |
| One-shot strategy, aimed at a specific pathology | Diverse and complementary strategies aimed at a network of issues/determinants |
| Directive and persuasive strategies enforced in target groups | Facilitating and enabling approaches by incentives offered to the population |
| Focused mostly on individuals | Focused on a person's health status and environment |
| Led by professional groups from health disciplines | Led by non-professional organizations, civic groups, local, municipal, regional, and national governments |

Source: Shah CP. Public Health and Preventive Medicine in Canada, 5th ed. Toronto: Elsevier, 2003

## Healthy Public Policy

- purpose: to create a supportive environment to enable people to lead healthy lives, thereby making healthy choices easier for citizens
- governments and non-governmental agencies need to consider the cost and acceptability of proposed public health interventions (i.e. more invasive or costly measures should be justified by the extent of beneficial impacts on people's lives)
- the Nuffield Intervention Ladder provides one way of ranking the level of intrusion and hence a need for proportionate benefit of health promotion interventions at a population level



**Electronic Cigarettes for Smoking Cessation**
Cochrane Database of Systematic Reviews 2016;13:9
There is evidence from two trials that ECs help smokers to stop smoking in the long term compared with placebo ECs. However, the small number of trials, low event rates and wide confidence intervals around the estimates mean that our confidence in the result is rated 'low' by GRADE standards. The lack of difference between the effect of ECs compared with nicotine patches found in one trial is uncertain for similar reasons. None of the included studies (short- to mid-term, up to two years) detected serious adverse events considered possibly related to EC use. The most commonly reported adverse effects were irritation of the mouth and throat. The long-term safety of ECs is unknown. In this update, we found a further 15 ongoing RCTs which appear eligible for this review.



**A Snapshot Of The Opioid Crisis In Canada**
Canada is experiencing a crisis of opioid-related overdose and death. The rate of opioid-related death in Ontario nearly tripled between 2000 and 2015, reaching a peak rate of 53.1 deaths per million Ontarians in 2015. Individuals aged 25 to 34 years old are at the greatest risk of overdose death (1 in 6 deaths), but rates have increased for all adult ages. Deaths are most commonly unintentional. Heroin, fentanyl, and hydromorphone are most commonly involved. The highest rates of opioid-related overdose and death are found in British Columbia. An estimated 300 per million British Columbians died in relation to opioid use in 2017. More died from opioids than homicide, motor vehicle accidents, and suicide combined. In 2017, deaths from opioids in Ontario ~1250, deaths from motor vehicle accidents ~450. Fentanyl or a fentanyl analogue was involved in more than 70% of cases, increased from 55% in 2016.
Sources: J Addict Med. Measuring the Burden of Opioid-related Mortality in Ontario, Canada. Latest Trends in Opioid-Related Deaths in Ontario: 1991 to 2015, Toronto: Ontario Drug Policy Research Network. Health Canada. March 2018.

- methods
  - fiscal: imposing additional costs (e.g. taxes on tobacco and alcohol)
  - legislative: implementing legal deterrents (e.g. smoking bans, legal alcohol drinking age)
  - social: improving health beyond providing universally funded health care (e.g. providing affordable housing)

Source: International Conference on Health Promotion, Adelaide, South Australia (1998)

## Behaviour Change

- behaviour is a result of three factors
  1. predisposing factors: knowledge, attitude, beliefs, values, intentions
  2. enabling factors: skills, supports
  3. reinforcing factors: health care professionals and the social context of family and community
- health education serves to: increase knowledge and skills and promote healthy behaviours

## Health Belief Model (1975)

- a psychological model adapted over time to explain and predict individual short- and long-term health behaviours based on one's beliefs and attitudes
- based on the assumption that one will adopt a beneficial health behaviour if 3 beliefs are present:
  - the negative health outcome is avoidable
  - expects that the health outcome can be prevented if the recommended health behaviour is adopted
  - the individual can be successful in adopting the health behaviour
- six concepts:
  - four concepts influencing one's "readiness to act" – perceived susceptibility, perceived severity, perceived benefits, perceived barriers
  - cues to action: stimuli that can trigger health action
  - self-efficacy: confidence in one's ability to take a health action

## Stages of Change Model

- provides a framework in which the Health Belief Model is applied to facilitating behaviour change (e.g. quitting smoking)

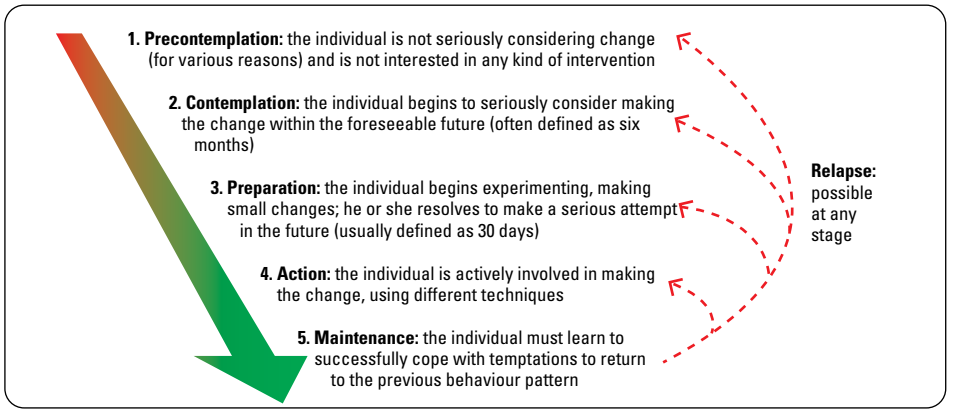



**Figure 3. Stages of change model**

Source: Prochaska JO, DiClemente CC, and Norcross JC. In Search of How People Change. Applications to Addictive Behaviours. Am Psychol 1992;47:1102-1114

## Risk Reduction Strategies

- risk reduction: lower the risk to health without eliminating it (e.g. avoiding sun to lower risk of skin cancer)
- harm reduction: a set of strategies aimed to reduce the negative consequences of drug use and other risky behaviours (e.g. needle exchange programs)

Source: Shah, CP. Concepts, Determinants, and Promotion of Health. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003

## Community Needs Assessment

- a community needs assessment studies a community's health gaps and pairs identification of that community's existing resources and strengths to find solutions to address those gaps. This assessment strongly values interviewing community members to gather their concerns and proposed solutions. Steps include:
  1. define the community and understand its history and demographic characteristics to formulate context for subsequent data collection
  2. understand what matters to community stakeholders, (i.e. interviews, surveys, focus groups)
  3. using evidence (e.g. mortality rate, feasibility), prioritize each concern
  4. identify barriers that may prevent a concern from being addressed and propose solutions using resources available to the community

# Measurements of Health and Disease in a Population

## MEASURES OF DISEASE OCCURRENCE

### Rates, Ratios, and Proportions
- a rate measures the frequency of an event in a defined population over a specific period of time (e.g. number of opioid overdoses in Canada in one year)
- a ratio compares the magnitude of one quantity to another (e.g. ratio of women to with lupus)
- a proportion is a ratio where the numerator is a part of the denominator (e.g. proportion of deliveries complicated by placental abruption)

### Incidence Rate
- number of new cases in a population over a specific period of time

### Prevalence
- total number of cases in a population over a defined period of time
- two forms of prevalence
  - point prevalence: assessed at one point in time
  - period prevalence: assessed over a period of time, therefore including new cases and excluding cases that terminate (cure or death)
- a function of the incidence rate and disease duration from onset to termination
- favours the inclusion of chronic over acute cases and may underestimate disease burden if those with short disease duration are missed
- prevalence estimates are useful for measuring disease burden and therefore help in the planning of facilities and services

### Age Standardized Rate
- adjustment of the crude rate of a health-related event using a "standard" population
- standard population is one with a known number of persons in each age and sex group
- standardization prevents bias which could be made by comparing crude rates from two dissimilar populations (e.g. crude death rates over a number of decades are not comparable as the population age distribution has changed with time)
- this allows for the calculation of a Standardized Mortality Ratio (SMR), where SMR = (observed number of deaths)/(expected number of deaths)

**Top 5 Causes of DALYs in Canada, 2010**
1. Ischemic Heart Disease
2. Low Back Pain
3. Lung Cancer
4. Major Depressive Disorder
5. Other Musculoskeletal

## MEASURES OF MORTALITY

### Life Expectancy
- the expected number of years to be lived by a newborn based on age-specific mortality rates at a selected time

### Crude Death Rate
- mortality from all causes of death per 1000 in the population

### Infant Mortality Rate (IMR)
- number of reported deaths among children <1 yr of age during a given time period divided by the number of reported live births during the same time period and expressed as per 1000 live births per year

### Maternal Mortality Rate (MMR)
- "number of deaths of women during pregnancy and due to puerperal causes […] per 1000 live births in the same year"

**Principles of Standardization**
- When comparing a health measure (e.g. mortality) between two populations (or the same population at different time points) that differ in characteristics known to influence that outcome (e.g. age), standardization is used to control for the effect of that factor
- Standardization is either direct or indirect
- Indirect standardization is expressed as standardized outcome ratio. For example, Standardized Mortality Ratio (SMR) is calculated using age specific rates for a reference population, as well as age structure and total cases for a sample/known population. (e.g. an SMR of 100 signifies that deaths are at the expected level, a SMR of 110 indicates a death rate 10% higher than expected)
- Direct standardization is expressed as a rate (i.e. using age specific rates in a known/sample population against a standard population)

## MEASURES OF DISEASE BURDEN

### Potential Years of Life Lost (PYLL)
- calculated for a population using the difference between the actual age at death and a standard/expected age at death
- increased weighting of mortality at a younger age

### Disability Adjusted Life Year (DALY)
- life expectancy weighted by amount of disability experienced, where 0 = perfect health and 1= death
- both premature death and time spent with disability accounted for; these disabilities can be physical or mental
- used to assess burden of diseases in a population

### Quality Adjusted Life Year (QALY)

- years of life weighted by quality (utility is a proxy for quality), ranging from 0 (= death) to 1 (= perfect health). Weights are assigned based on large studies that assessed the effect of various conditions on quality of life (e.g. blindness = 0.3)
- it is possible to have "states worse than death" for example QALY <0 for extremely serious conditions
- usually used as an economic measure to assess the value for money of medical interventions

For additional rate calculations see *Steps to Control an Outbreak*, PH21
Consult the Public Health Agency of Canada for examples and latest statistics
http://www.phac-aspc.gc.ca/cphorsphc-respcacsp/2008/fr-rc/cphorsphc-respcacsp06b-eng.php
Sources: Shah, CP. Health Indicators and Data Sources. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003
The Association of Faculties of Medicine of Canada Public Health Educators' Network. Methods: Measuring Health. AFMC Primer on Population Health

# Epidemiology

### Population

- a defined collection of individuals/regions/institutions/etc. (e.g. individuals defined by geographic region, sex, age)

### Sample

- a selection of individuals from a population
- types
  - random: all members are equally likely to be selected
  - systematic: an algorithm is used to select a subset
  - stratified: population is divided into subgroups that are each sampled
  - cluster: grouped in space/time to reduce costs
  - convenience: non-random inclusion, for populations that are difficult to reach (e.g. people with precarious living conditions)



**SPIN**: use a **SP**ecific test to rule **IN** a hypothesis. Note that specific tests have very few false positives. If you get a positive test, it is likely a true positive
**SNOUT**: use a **SEN**sitive test to rule **OUT** a hypothesis. Note that sensitive tests have very few false negatives. If you get a negative test, it is likely a true negative

### Sample Size

- increasing the sample size increases the statistical precision of the observed estimate, resulting in more narrow confidence intervals
- increasing the sample size decreases the probability of type I and type II errors
- increasing sample size does not alter the risk of bias/confounding

### Bias

- systematic error leading to an incorrect estimate of the true association between exposure and outcome
- can occur at several points in study execution (e.g. collection, analysis, interpretation, publication, or review of data)
  - **selection bias**: a systematic error in the recruitment or retention of study participants
- **Berkson's bias** occurs in a case-control study using hospitalized controls, as they may not be a representative sample of the population due to the complexity that led to their hospital admission
- **non-response bias** occurs when participants differ from non-participants in a study, in that those who volunteer may be more healthy
- **loss to follow-up bias** occurs when dropout rates differ between study groups and patients who dropped out are different from those who did not
  - information bias: the way in which information is collected about study participants is inadequate
- **recall bias** occurs when individuals with disease may be more likely to incorrectly recall/believe they were exposed to a possible risk factor than those who are free of disease
- **interviewer bias** occurs when interviewers are unblinded to outcome status and this knowledge biases their behaviour
  - outcome identification bias
- **observer bias** occurs when knowledge of exposure status (e.g., race, gender) biases the observer towards a diagnosis; this occurs more commonly with subjective diagnoses like those found in psychiatry

### Confounder

- a variable that is related to both the exposure and outcome but is not a mediator in the exposure-outcome relationship
- distorts the estimated effect of an exposure if not accounted for in the study design/analysis (e.g. late maternal age could be a confounder in an investigation of birth order >4 and risk of developing Trisomy 21)
- randomization, stratification, matching, and regression modelling can help minimize confounding effects

Source: The Association of Faculties of Medicine of Canada Public Health Educators' Network. Assessing Evidence and Information. AFMC Primer on Population Health

# Interpreting Test Results

TP = True positive TN = True negative FP = False positive FN = False negative

| | | Disease | |
|---|---|---|---|
| | | Present | Negative |
| Test Result | Positive | TP | FP |
| | Negative | FN | TN |

Sensitivity = TP/(TP+FN)
Specificity = TN/(TN+FP)

**Likelihood Ratio (LR)**
- Likelihood that a given test result would be expected in a patient with disease compared with the likelihood that the same result would be expected in a patient without disease
- LR+ indicates how much the probability of disease increases if the test is positive
- LR- indicates how much the probability of disease decreases if the test is negative

$$\textbf{LR+} = \frac{\text{Sensitivity}}{1 - \text{Specificity}} = \frac{[TP/(TP+FN)]}{[FP/(TN+FP)]} \qquad \textbf{LR–} = \frac{1 - \text{Sensitivity}}{\text{Specificity}} = \frac{[FN/(TP+FN)]}{[TN/(TN+FP)]}$$

**Positive Predictive Value (PPV)**
- Proportion of people with a positive test who have the disease

$$\textbf{PPV} = \frac{TP}{TP + FP}$$

**Negative Predictive Value (NPV)**
- Proportion of people with a negative test who are free of disease

$$\textbf{NPV} = \frac{TN}{TN + FN}$$

| | | Advanced Neoplasia | |
|---|---|---|---|
| | | Present | Negative |
| Test Result | Positive | 68 | 147 |
| | Negative | 216 | 2234 |
| | Total | 284 | 2381 |

**Sensitivity** = 68/284 = 23.9%
**Specificity** = 2234/2381 = 93.8%

$$\textbf{LR+} = \frac{0.239}{1 - 0.938} = 3.85$$

$$\textbf{LR–} = \frac{1 - 0.239}{0.938} = 0.81$$

$$\textbf{PPV} = \frac{68}{(68+147)} = 31.6\%$$

$$\textbf{NPV} = \frac{2234}{(2234+216)} = 91.2\%$$

**Figure 4. Interpreting test results: Practical example using FOBT testing in advanced colon cancer**
Source: Numbers from Collins J, Lieberman D, Durbin T, et al. Accuracy of screening for fecal occult blood on a single stool sample obtained by digital rectal examination: a comparison with recommended sampling practice. Ann Intern Med 2005;142:81-85

## Sensitivity
- proportion of people with disease who have a positive test

## Specificity
- proportion of people without disease who have a negative test

## Pre-Test Probability
- the probability a particular patient has a given disease before a test/assessment results are known

## Post-Test Probability
- a revision of the probability of disease after a patient has been interviewed/examined/tested
- calculation process can be explicit using results from epidemiologic studies, knowledge of the accuracy of tests, and a nomogram/Bayes' theorem
- the post-test probability from clinical examination is the basis of consideration when ordering diagnostic tests or imaging studies
  - after each iteration the resultant post-test probability becomes the pre-test probability when considering new investigations

**Figure 5. Understanding sensitivity and specificity**

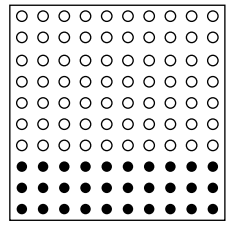



**Figure 5a. Hypothetical population**

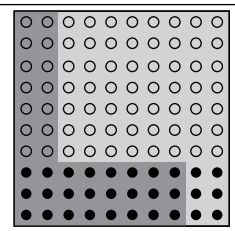



**Figure 5b. Results of diagnostic test on hypothetical population**

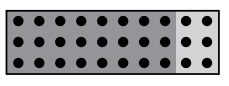


**Figure 5c. Sensitivity of test (e.g. 24/30 = 80% sensitive)**

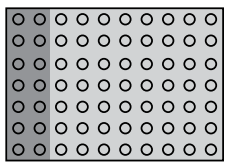


**Figure 5d. Specificity of test (e.g. 56/70 = 80% specific)**

Source: Loong TW. Understanding sensitivity and specificity with the right side of the brain *BMJ* 2003;327:716-719

Sensitivity and specificity are characteristics of the test
LR depends on the test characteristics, not the prevalence
PPV and NPV depend on the prevalence of the disease in the population

# Effectiveness of Interventions

## Effectiveness, Efficacy, Efficiency

- three measurements indicating the relative value (beneficial effects vs. harmful effects) of an intervention
  - efficacy: the extent to which a specific intervention produces a beneficial result under ideal conditions (e.g. RCT)
- ideal conditions include adherence, close monitoring, access to health resources, etc.
  - effectiveness: measures the benefit of an intervention under usual conditions of clinical care
- considers both the efficacy of an intervention and its actual impact on the real world, taking into account access to the intervention, whether it is offered to those who can benefit from it, its proper administration, acceptance of intervention, and degree of adherence to intervention
  - efficiency: a measure of economy of an intervention with known effectiveness
- considers the optimal use of resources (e.g. money, time, personnel, equipment, etc.)

**Disease** (e.g. lung cancer)

| **Exposure** (e.g. smoking) | **Present** | **Absent** | **Total** |
|---|---|---|---|
| **Present** | A | B | A + B |
| **Absent** | C | D | C + D |
| **Total** | A + C | B + D | A + B + C + D |

**Case-Control Study**

$$\text{odds ratio (OR)}^* = \frac{A}{C} \div \frac{B}{D} = \frac{A \times D}{B \times C}$$

**Cohort Study**

$\frac{A}{A+B}$ = incidence rate of health outcome in exposed $\frac{C}{C+D}$ = incidence rate of health outcome in non-exposed

$$\text{relative risk (RR)}^{**} = \frac{A}{A+B} \div \frac{C}{C+D} \qquad \text{attributable risk (AR)}^{***} = \frac{A}{A+B} - \frac{C}{C+D}$$

*Ratio of the odds in favour of the health outcome among the exposed to the odds in favour among the unexposed
**Ratio of the risk of a health outcome among exposed to the risk among the unexposed
***Rate of health outcome in exposed individuals that can be attributed to the exposure

**Figure 7. Measures of effect by study type**

## Number Needed to Treat (NNT)

- number of patients who need to be treated to achieve one additional favourable outcome
- only one of many factors that should be taken into account in clinical or health system decision making (e.g. must take into account cost, ease, feasibility of intervention)
  - a condition with death as a potential outcome can have a higher NNT (and be acceptable), as compared to an intervention to prevent an outcome with low morbidity, in which a low NNT would be necessary

## Number Needed to Harm (NNH)

- number of patients who, if they received the experimental treatment, would lead to one additional patient being harmed, compared with patients who received the control treatment

## Adherence (formerly compliance)

- degree to which a patient's behaviour and lifestyle concords with the recommendations of healthcare providers (e.g. the extent to which a patient takes medications as directed)

## Coverage

- extent to which the services rendered cover the potential need for these services in a community

Sources: Shah, CP. Health Indicators and Data Sources. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003
The Association of Faculties of Medicine of Canada Public Health Educators' Network. Assessing Evidence and Information. AFMC Primer on Population Health

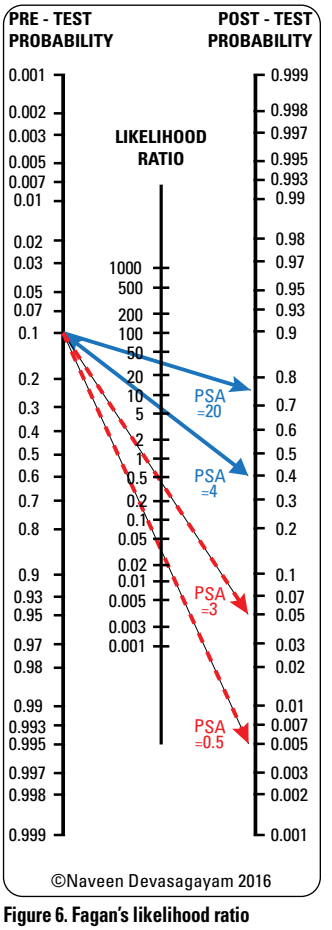



**Figure 6. Fagan's likelihood ratio nomogram: Practical example using PSA levels to calculate post-test probability of prostate cancer**

Source: Modified from Holmstrom B, Johansson M, Bergh A, et al. Prostate specific antigen for early detection of prostate cancer: longitudinal study. *BMJ* 2009;339:b3537

**Equations to Assess Effectiveness**
CER = control group event rate
EER = experimental group event rate
RR = EER/CER
ARR = CER – EER
NNT = 1/ARR

**Beware**
Do not be swayed by a large RR or odds ratio, as it may appear to be large if event rate is small to begin with. In these cases AR is more important (e.g. a drug which lowers an event which occurs in 0.1% of a population to 0.05% can boast a RR of 50%, and yet the AR is only 0.05%, which is not nearly as impressive)

**NNT**
Consult http://www.thennt.com for quick summaries of evidence-based medicine (includes NNT, LR, and risk assessments)

# Types of Study Design

## Qualitative vs. Quantitative

**Table 6. Qualitative vs. Quantitative Study Designs**

| Qualitative | Quantitative |
|---|---|
| Often used to generate hypothesis (Why? What does it mean?) | Often tests hypothesis (What? How much/many?) |
| "Bottom up" approach | "Top down" approach |
| Observation → pattern → tentative hypothesis → theory | Theory → hypothesis → observation → confirmation |
| Sampling approach to obtain representative coverage of ideas, concepts, or experiences | Sampling approach to obtain representative coverage of people in the population |
| Narrative: rich, contextual, and detailed information from a small number of participants | Numeric: frequency, severity, and associations from a large number of participants |

Source: Adapted from http://phprimer.afmc.ca
Source: The Association of Faculties of Medicine of Canada Public Health Educators' Network. Assessing Evidence and Information. AFMC Primer on Population Health

### Quantitative Research Methods

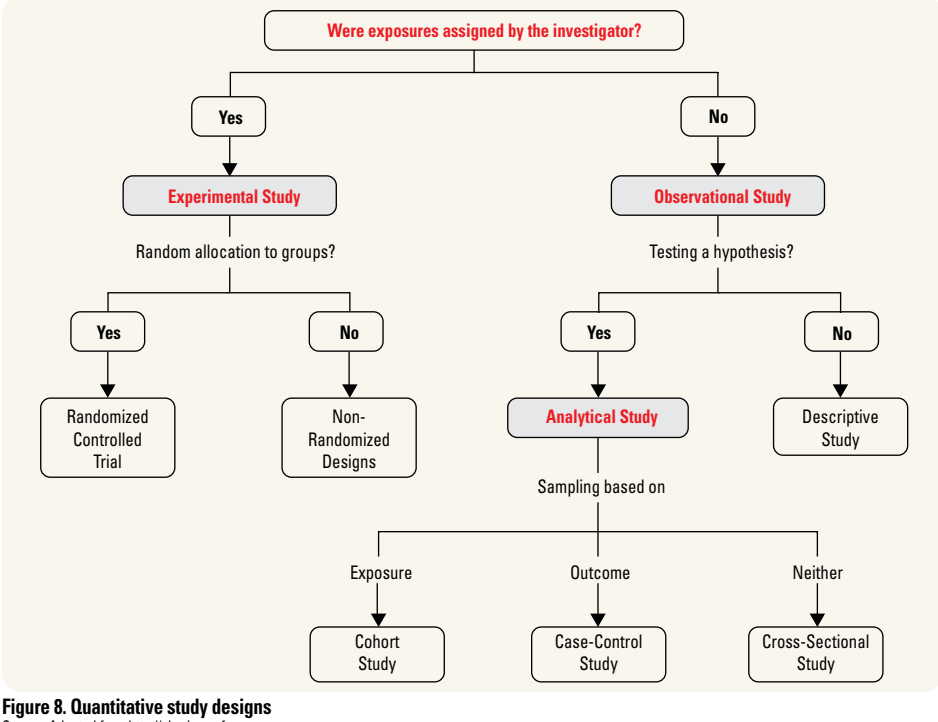



**Figure 8. Quantitative study designs**
Source: Adapted from http://phprimer.afmc.ca

**Formulating a Research Question**

**PICO**
**P**opulation/**P**atient Characteristics
**I**ntervention/Exposure of Interest
**C**omparison Group or Control Group
**O**utcome that you are trying to prevent or achieve

## Observational Study Designs

- observational studies involve neither the manipulation of the exposure of interest nor randomization of the study participants
- there are two main subtypes of observational studies: descriptive and analytic studies

### Descriptive Studies

- describe the events and rates of disease with respect to person, place, and time; estimates disease frequency and time trends
- can be used to generate an etiologic hypothesis and for policy planning

### Analytic Studies

- observational studies used to test a specific hypothesis
- includes ecological studies, cohort studies, case-control studies, and cross-sectional studies

An ecological fallacy is an erroneous conclusion made when extrapolating population level data to explain phenomena occurring in individuals. An example of an ecological fallacy would be concluding that red wine drinking leads to lower risk of death from CVS disease based on an ecological study showing that countries with a higher rate of red wine consumption have a lower rate of death from CVS causes

**Table 7. Observational Study Designs**

| Type of Study | Ecological | Cross-Sectional | Case-Control | Cohort |
|---|---|---|---|---|
| **Definition** | Units of analysis are populations or groups of people, rather than individuals | Use individual data on exposures and outcomes gathered at the same time | Samples a group of people who already have a particular outcome (cases) and compares them to a similar sample group without that outcome (controls) | Subjects are sampled and, as a group, classified on the basis of presence or absence of exposure to a particular risk factor |
| **Subjects** | Aggregated groups (e.g. cities) | Sample of a population | Two or more samples of individuals with and without the outcome(s) of interest (i.e. cases and controls) | One or more cohorts<br>Cohort: group of people with common characteristics (e.g. year of birth, region of residence)<br>Divided into measured exposed vs. non-exposed groups |
| **Methods** | Descriptions of the average exposure or risk of disease for a population<br>Can use regression models to test associations between area-level predictors and aggregate outcomes | Collect information from each person at one particular time<br>Tabulate the numbers in groups (e.g. by presence or absence of disease/factor of interest)<br>Make tables and compare groups<br>Estimate prevalence<br>Use regression models to test associations between predictors and outcomes of interest | Select sample of cases of a specific disease during a specific time frame<br>Representative of spectrum of clinical disease<br>Select control(s)<br>Represent the general population<br>To minimize risk of bias, may select more than one control group and/or match controls to cases (e.g. age, gender)<br>Assess past exposures (e.g. EMR, questionnaire)<br>Association can be concluded between the risk factor and the disease (odds ratio) | Collect information on factors from all persons at the beginning of the study<br>Subjects are followed for a specific period of time to determine development of disease in each exposure group<br>Prospective: measuring from the exposure at present to the future outcomes<br>Retrospective: measuring forward in time from exposures in the past to later outcomes<br>Use statistical models to test associations between exposures and disease or other measured outcomes<br>Provides estimates of incidence, relative risk, attributable risk |
| **Advantages** | Quick, easy to do<br>Uses readily available data<br>Generates hypothesis | Determines association between variables<br>Quick and uses fewer resources<br>Surveys with validated questions allows comparison between studies | Often used when disease in population is rare (less than 10% of population) due to increased efficiency or when time to develop disease is long<br>Less costly and time consuming | Shows an association between risk factor(s) and outcome(s)<br>Stronger evidence for causation<br>Can consider a variety of exposures and outcomes |
| **Disadvantages** | Poor generalizability to individual level (not direct assessment of causal relationship)<br>Ecological fallacy: an incorrect inference from groups to individuals<br>Confounding | Does not allow for assessment of temporal relationship or offer strong evidence for causation between variables<br>Confounding<br>Selection bias<br>Recall bias<br>(see *Bias*, PH10) | Recall bias<br>(see *Bias*, PH10)<br>Confounding<br>Selection bias for cases and controls<br>Only one outcome can be measured | Confounding may occur due to individuals self-selecting the exposure, or unknown/unmeasured factors are associated with the measured exposure and outcome<br>Cost and duration of time needed to follow cohort<br>Selection bias |
| **Examples** | A study looking at the association between smoking rates and lung cancer rates in different countries at the population level without individual data on both factors | A study that examines the distribution of BMI by age in Ontario at a particular point in time | A famous case control study published by Sir Richard Doll demonstrated the link between tobacco smoking exposure and lung cancer cases at the individual level | A famous cohort study is the Framingham Heart Study, which assessed the long-term cardiovascular risks of diet, exercise, medications such as ASA, etc. |

Sources: Shah, CP. Measurement and Investigation. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003
The Association of Faculties of Medicine of Canada Public Health Educators' Network. Assessing Evidence and Information. AFMC Primer on Population Health
Rothman KJ, Greenland SG, Lash TL. Modern Epidemiology, 3e. Philadelphia: Wolters Kluwer, 2012

# Experimental Study Designs

- not discussed here are non-randomized control trials (e.g. allocation by clinic or other non-random basis – performed when randomization is not possible)

## RANDOMIZED CONTROLLED TRIAL (RCT)

### Definition
- participants are assigned by random allocation to two or more groups, one of which is the control group, the other group(s) receive(s) an intervention

### Participants
- individuals are selected using explicit inclusion/exclusion criteria and recruitment targets are guided by sample size calculations

### Methods
- random allocation of individuals into two or more treatment groups through a centralized concealed process
- method of assessment to reduce bias
  - single-blind: participant does not know group assignment (intervention or placebo)
  - double-blind: participant and observer both unaware of group assignment
  - triple-blind: participant, observer, and analyst unaware of group assignment
- control group receives standard of care or placebo if no standard of care exists
- one or more groups receive(s) the intervention(s) under study
- baseline covariates and outcome(s) are measured and the groups are compared
- all other conditions are kept the same between groups

### Advantages
- "gold standard" of studies, upon which the practice of EBM is founded
- provides the strongest evidence for effectiveness of intervention
- threats to validity are minimized with sufficient sample size and appropriate randomization
- randomization is one of few methods that can eliminate confounding (including unmeasured confounders) and self-selection bias
- allows prospective assessment of the effects of intervention

### Disadvantages
- some exposures are not amenable to randomization (e.g. cannot randomize participants to poverty/wealth or to harmful exposures such as smoking) due to ethical or feasibility concerns
- can be difficult to randomly allocate groups (e.g. communities, neighbourhoods)
- difficult to study rare events, since RCTs would require extremely large sample sizes
- contamination, co-intervention, and loss to follow-up can all limit causal inferences
- can have poor generalizability (e.g. when trial participants are healthier than the average patient population)
- costly

Sources: Shah, CP. Measurement and Investigation. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003
The Association of Faculties of Medicine of Canada Public Health Educators' Network. Assessing Evidence and Information. AFMC Primer on Population Health

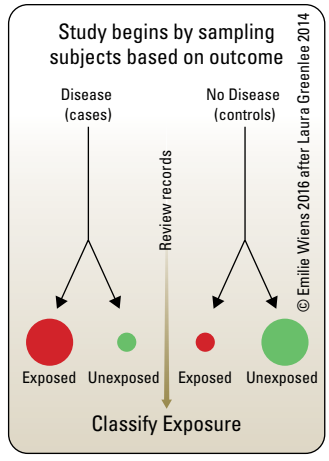



**Figure 9. Case-control study**
Adapted from http://phprimer.afmc.ca

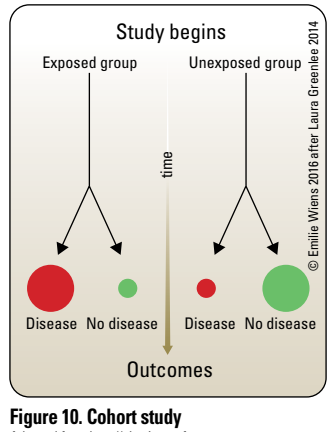



**Figure 10. Cohort study**
Adapted from http://phprimer.afmc.ca

**Analysis**
**Per-Protocol Analysis (PP)**
Strategy of analysis in which only patients who complete the entire study are counted towards the results

**Intention-to-Treat Analysis (ITT)**
When groups are analyzed exactly as they existed upon randomization (i.e. using data from all patients, including those who did not complete the study)

An example of an RCT is the SPARCL trial, which demonstrated intense lipid-lowering with atorvastatin reduces the risk of cerebro- and cardiovascular events in patients with and without carotid stenosis when compared to placebo

An example of a meta-analysis is one that compares the effects of ACE inhibitors, CCBs, and other antihypertensive agents on mortality and major cardiovascular events by compiling and analyzing data from a full set of reported RCTs

# Summary Study Designs

## META-ANALYSIS

### Definition
- a form of statistical analysis that aggregates all relevant studies addressing the same research question in order to increase statistical precision

### Participants
- all the studies identified through a systematic literature review

### Methods
- selection of relevant studies from the published literature which meet quality criteria
- statistical models used to combine the results of each independent study
- provides a summary statistic of overall results as well as graphic representation of included studies (forest plot)

### Advantages
- attempts to overcome the problem of reduced power due to small sample sizes of individual studies
- can address questions (e.g. subgroup analyses) that the original studies were not powered to answer

### Disadvantages
- studies may be heterogenous and therefore inappropriate to combine (e.g. different patient populations, exposure classification/measurement, outcome assessment)
- reliance on published studies may increase the potential conclusion of an effect as it can be difficult to publish studies that show no significant results (publication bias)

Sources: Shah, CP. Measurement and Investigation. Public Health and Preventive Medicine in Canada, 5e. Toronto: Elsevier, 2003
The Association of Faculties of Medicine of Canada Public Health Educators' Network. Assessing Evidence and Information. AFMC Primer on Population Health

# Methods of Analysis

## Distributions

- a distribution describes the frequency at which each value (or category) occurs in a study population
- distributions can take characteristic shapes. i.e., normal (Gaussian) or non-normal (binomial, gamma, skewed, etc.)
- characteristics of the normal distribution
  - mean = median = mode
  - 67% of observations fall within one standard deviation of the mean
  - 95% of observations fall within two standard deviations of the mean
- measures of central tendency
  - **mean**: sum of each observation's data (e.g. ages) divided by total number of observations
  - **median**: value of the 50th percentile; a better reflection of the central tendency for a skewed distribution
  - **mode**: most frequently observed value in a series
- measures of dispersion
  - **range**: the largest value minus the smallest value
  - **variance**: a measure of the spread of data
  - **standard deviation**: the average distance of data points from the mean (the positive square root of variance)
- given the mean and standard deviation of a normal or binomial distribution curve, a description of the entire distribution of data is obtained

## Data Analysis

### Statistical Hypotheses

- null (Ho)
  - the default hypothesis; often states there is no relationship between two variables
- alternative (H1)
  - the hypothesis that we are interested in; often states there is a relationship between two variables
  - we can find evidence against Ho but we can never 'prove' H1

### Type I Error (α Error)

- the null hypothesis is falsely rejected (i.e. concluding an intervention X is effective when it is not, or declaring an observed difference to be real rather than by chance)
- the probability of this error is denoted by the p-value
- studies tend to be designed to minimize this type of error, since a type I error can have larger clinical significance than a type II error

### Type II Error (β Error)

- the null hypothesis is falsely accepted (i.e. stating intervention X is not effective when it is, or declaring an observed difference/effect to have occurred by chance when it is present)
- by convention a higher level of error is often accepted for most studies
- can also be used to calculate statistical power

### Power

- probability of correctly rejecting a null hypothesis when it is in fact false (i.e. the probability of finding a specified difference to be statistically significant at a given p-value)
- power increases with an increase in sample size
- power = 1 – β, and is therefore equal to the probability of a true positive result

### Statistical Significance

- the probability that the statistical association found between variables is due to random chance alone (i.e. there is no association)
- the preset probability is set sufficiently low that one would act on the result; frequently $p<0.05$
- when statistical tests result in a probability less than the preset limit, the results are said to be statistically significant (denoted by the α-value)

### Clinical Significance

- measure of clinical usefulness (e.g. 1 mmHg BP reduction may be statistically significant, but may not be clinically significant)
- depends on factors such as cost, availability, patient adherence, and side effects in addition to statistical significance

### Confidence Interval (CI)

- provides a range of values within which the true population result (e.g. the mean) lies, bounded by the upper and lower confidence limits
- frequently reported as 95% CI (i.e. if this study were repeated 100 times, estimates would fall within the 95% CI 95 out of 100 times)

Consult the Cochrane Library of Systematic Reviews (http://www.cochranelibrary.com) for high-quality systematic reviews and meta-analyses

**Example Calculation**
Data set: 17, 14, 17, 10, 7
Mean = (17 + 14 + 17 + 10 + 7) ÷ 5 = 13
Median (write the list in order, median is the number in the middle)
= 7, 10, 14, 17, 17 = 14
Mode (number repeated more often) = 17
Range = 17- 7 = 10
Variance = $[(17-13)^2 + (14-13)^2 + (17-13)^2 + (10-13)^2 + (7-13)^2] \div 5 = 19.5$
Standard Deviation = √variance = √19.5 = 4.42

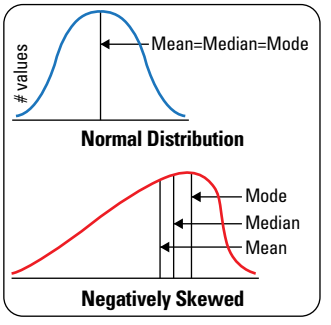



**Figure 11. Distribution curves**

**Type I (α) Error**
"**T**here **I**s **A**n **E**ffect" where in reality there is none

A wider confidence interval implies more variance than a tighter confidence interval given the same critical value

### Data
- information collected from a sample of a population
- there are 4 overall levels of measurement for quantitative data
  - categorical (e.g. blood type, marital status)
  - ordinal (e.g. low, medium, high)
  - interval (e.g. °C, time of day)
  - ratio (e.g. serum cholesterol, hemoglobin, age)

### Validity/Accuracy (of a measurement tool)
- how closely a measurement reflects the entity it claims to measure

### Reliability/Precision
- how consistent multiple measurements are when the underlying subject of measurement has not changed
- may be assessed by different observers at the same time (inter-rater reliability) or by the same observer under different conditions (test-retest reliability)

### Internal Validity
- degree to which the findings of the sample truly represent the findings in the study population
- dependent on the reliability, accuracy, and absence of other biases

### External Validity (i.e. Generalizability)
- degree to which the results of the study can be generalized to other situations or populations

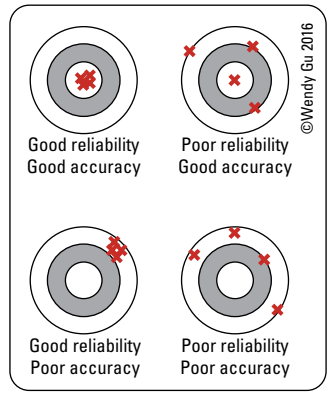



**Figure 12. Validity vs. reliability**

## Common Statistical Tests

**Table 8. Statistical Tests**

| | Two-sample Z-Test | Analysis of Variance (ANOVA) | Chi-Squared Test ($\chi^2$) | Linear Regression | Logistic Regression | Pearson product-moment correlation (Pearson's r) |
|---|---|---|---|---|---|---|
| **What are you trying to show?** | | | | | | |
| | Compare the mean values of an outcome variable between two groups (e.g. difference in average BP between men and women) | Compare the mean values of an outcome variable between two or more groups (e.g. difference in average BP between persons in three towns) | Test the correspondence between a theoretical frequency distribution and an observed frequency distribution (e.g. if one sample of 20 patients is 30% hypertensive and another comparison group of 25 patients is 60% hypertensive, a chi-squared test determines if this variation is more than expected due to chance alone) | Looks at associations between two or more variables (e.g. age and blood pressure) | Shows how a change in one explanatory variable affects the status (e.g. ill vs. non-ill) of the outcome variable | Assesses the strength of the linear relationship between two variables. Ranges from -1 (negative association, i.e. increases in one variable are associated with decreases in another) to 1 (positive association, increases in one variable are associated with increases in the other). A correlation of 0 indicates no relationship |
| **What kind of variables do you measure?** | | | | | | |
| **Dependent Variable** | Continuous data | Continuous data | Categorical (2 or more)/ordinal | Continuous | Categorical (outcomes usually dichotomous) | Continuous |
| **Independent Variable** | Dichotomous | Categorical/ Ordinal (2 or more) | Categorical/Ordinal (2 or more) | Continuous/ Ordinal/ Categorical | Continuous/ Ordinal/ Categorical | Continuous |
| **Assumptions** | Data follow a normal/t-distribution<br>Equal variances<br>Data are independent | "Normal" distribution of dependent variable's error term<br>Data are independent | Expected counts must be at least 5 for all cells in n by n table<br>Data are independent | Dependent variable's error term has "normal" distribution<br>Linear relationship between variables<br>Homoskedasticity<br>No influential values<br>Data are independent | Linearity (on logit scale)<br>No influential values<br>Model has adequate goodness-of-fit<br>Data are independent | Underlying relationship is linear<br>Data for both variables are normally distributed<br>Data are independent |

**What's the difference between Pearson and Spearman correlation?**
Different types of correlation are used for different levels of measurement. Pearson is for continuous and Normal data, Spearman is for ordinal or non-Normal data. There are other forms of correlation for other levels of measurement (e.g. Tetrachoric/polychoric)

# Causation

### Criteria for Causation (Bradford Hill Criteria)

1. **strength of association**: the frequency with which the factor is found in the disease, and the frequency with which it occurs in the absence of disease
2. **consistency**: is the same relationship seen with different populations or study design?
3. **specificity**: is the association particular to your intervention and measured outcome?
4. **temporal relationship**: did the exposure occur before the onset of the disease?
5. **biological gradient**: finding a dose response relationship between the exposure-outcome
6. **biological plausibility**: does the association/causation make biological sense?
7. **coherence**: can the relationship be explained/accounted for based on what we know about science, logic, etc.?
8. **experimental evidence**: does experimental evidence support the association (e.g. is there improvement?)
9. **analogy**: do other established associations provide a model for this type of the relationship?

**Note**: Not all criteria must be fulfilled to establish scientific causation, and the modern practice of EBM emphasizes 'experimental evidence' as superior to other criteria for experimental causation review. However, many causation questions in health cannot be answered with experimental methods.

Source: Bradford Hill A. The environment and disease: association or causation. Proc R Soc Med 1965; 58(5): 295-300.

# Assessing Evidence

- critical appraisal is the process of systematically examining research evidence to assess validity, results, and relevance before using it to inform a decision

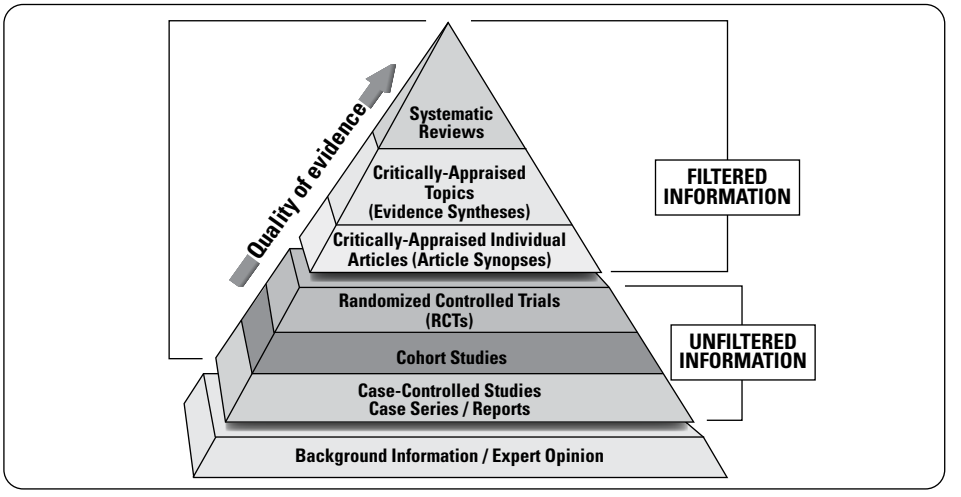



**Figure 13. Pyramid of pre-appraised evidence**

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**A. Are the results of the study valid?**

- see below for classifications of evidence that has already been assessed; see sidebar for assessing primary studies

**B. What are the results?**

- what was the impact of the treatment effect?
- how precise was the estimate of treatment effect?
- what were the confidence intervals and power of the study?

**C. Will the results help me in caring for my patients?**

- are the results clinically significant?
- can I apply the results to my patient population?
- were all clinically important outcomes considered?
- are the likely treatment benefits worth the potential harm and costs?

**Levels of Evidence: Classifications Cited in Guidelines/Consensus Statements**

Level I evidence: based on RCTs (or meta-analysis of RCTs) big enough to have low risk of incorporating FP or FN results

Level II evidence: based on RCTs too small to provide Level I evidence; may show positive trends that are non-significant, or have a high risk of FN results

Level III evidence: based on non-randomized, controlled or cohort studies; case series; case-controlled; or cross-sectional studies

Level IV evidence: based on opinion of respected authorities or expert committees, as published consensus conferences/guidelines

Level V evidence: opinions of the individuals who have written/reviewed the guidelines (i.e. Level IV evidence), based on experience/knowledge of literature/peer discussion

Notes: These 5 levels of evidence are not direct evaluations of evidence quality or credibility; they reflect the nature of the evidence. While RCTs tend to be most credible (with <III), level III evidence gains credibility when multiple studies from different locations and/or time periods report consistent findings. Level IV and V evidence reflects decision-making that is necessary but in the absence of published evidence.

**Figure 14. Levels of evidence classifications**
Note: This is only one method of classifying evidence. Various systems exist, but operate within the same premise that certain types of evidence carry more weight than others

# Health System Planning and Quality

## Continuous Quality Improvement

### Quality Improvement (QI)
- a means of evaluating and improving processes; focusing more on systems and systematic biases, which are thought to cause variation in quality
- measures to increase efficiency of action with the purpose of achieving optimal quality

### Quality Assurance
- process to guarantee the quality of health care through improvement and attainment of set standards
- **"five-stage process of quality assurance"** (Public Health and Preventative Medicine in Canada, Shah)
  1. formulation of working goals
  2. procedural changes to implement those goals
  3. regular comparison of current performance with original goals
  4. development of solutions to bring performance closer to goals
  5. documentation of quality assurance activities

### Quality Control
- a process of surveying the quality of all factors involved in the process to maintain standards

### Continuous Quality Improvement
- the process of ongoing service/product refinement via the vigilant review of expectant issues detrimental to the system and regular incorporation of improvements

### Quality Management
- combination of several processes (assurance, control, improvement) to maintain consistent quality

### Total Quality Management
- management principle for advancing quality while minimizing additional expenditures
- focuses on the entire system rather than discrete elements

### Audit
- methodical analysis of a quality system by quality auditors
- to determine whether quality processes and results comply with goals, and whether processes have been implemented effectively

### Systems Analyses Tools
1. **5 Whys**: brainstorming to simplify the process of change; continue asking 'why' until the root of the problem is discovered
2. **Ishikawa Diagrams** (i.e. Fishbone Diagrams): identify generic categories of problems that have an overall contribution on the effect
3. **Defect check sheets**: consider all defects and tally up the number of times the defect occurs
4. **Pareto Chart**: x vs. y chart; x-axis = defect categories, y-axis = frequency; plot cumulative frequency on the right y-axis; purpose is to highlight most important among large set of factors contributing to defects/poor quality

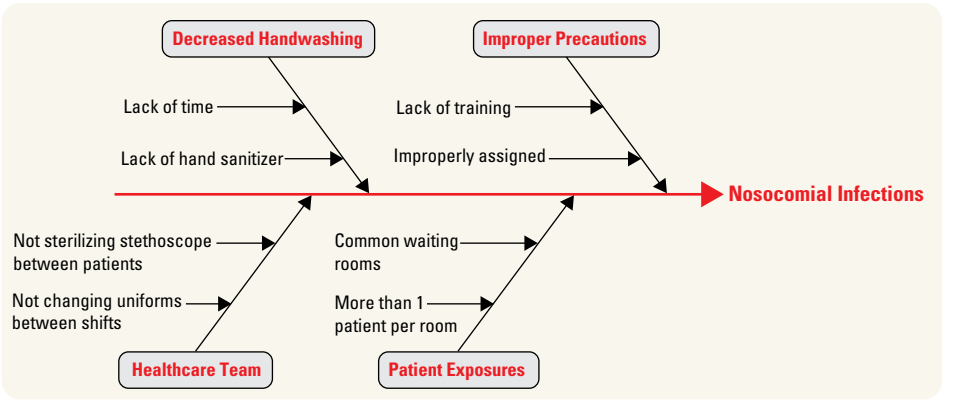



**Figure 15. Ishikawa diagram**

### Precede-Proceed Model
- tool for designing, implementing, and evaluating health interventions/programs

**Table 9. Precede-Proceed Model**

| PRECEDE Phase | PROCEED Phase |
|---|---|
| Phase 1 – Identify the ultimate desired result | Phase 5 – Implementation (design and conduct the intervention) |
| Phase 2 – Identify health issues and their behavioural and environmental determinants. Set priorities among them | Phase 6 – Process Evaluation (determine if the program is implemented as planned) |
| Phase 3 – Identify the predisposing, enabling, and reinforcing factors that affect the behaviours and environmental determinants | Phase 7 – Impact Evaluation (measure intermediate effects on the target population) |
| Phase 4 – Identify the administrative and policy factors that influence what can be implemented | Phase 8 – Outcome Evaluation (determine whether the original desired result was achieved) |

### Planning Cycles/Models
1. **APIE Planning Model**: *Assessment, Planning, Implementation, Evaluation*
2. **PDSA Planning Cycle**: *Plan, Do, Study, Act*

## Cost Analysis

### Cost Benefit Analysis (CBA)
- an analysis which compares the total expected costs with the total expected benefits of actions in order to choose the most profitable or beneficial options
- costs are controlled for inflation and market changes so that the effect of the change is evaluated over a consistent, preset financial value

### Cost Effectiveness Analysis (CEA)
- ratio of the change in cost (numerator) to change in effect (denominator) in response to a new strategy or practice
  - the numerator highlights the cost of the health gain
  - some examples of changes in effect (denominator) could be years of life gained or sight-years gained
  - the most commonly used outcome measure is quality-adjusted life years (QALY) (see *Quality Adjusted Life Year*, PH10)
- can be used where an extensive cost benefit analysis is not applicable or appropriate

# Managing Disease Outbreaks

## Definitions

### Outbreak
- incidence of new cases beyond the usual frequency of disease in a population or community in a given time

### Endemic
- consistent existence of infectious agent or disease in a given population or area (i.e. usual rate of disease)

### Epidemic
- an increase, often sudden, in cases of a disease above what is usually expected in a particular population (e.g. SARS epidemic)
- can occur due to a recent increase in the virulence or amount of an agent, introduction of a new agent to an area, enhanced mode of transmission of the agent, altered host response, and/or increased host susceptibility through more exposure or portals of entry

### Pandemic
- epidemic that has spread across international or intercontinental boundaries, affecting a large number of people

### Attack Rate
- proportion of an initially disease-free population that develops the disease over a specified time period
- = [(# of new cases of disease) / (initial population size)] * 100%

### Secondary Attack Rate
- the proportion of individuals who develop disease as a result of exposure to primary contacts during the incubation period
- = [(total # of cases - initial # of cases) / (# of susceptible individuals - initial # of cases)] * 100%
- measure of infectiousness, which reflects the ease of disease transmission

### Virulence
- measure of an infectious agent to cause significant sickness
- = (# of cases that are severely ill or died) / (total # of cases)

### Case-Fatality Rate (CFR)
- proportion of individuals with the disease who died as a result of the illness
- must be clearly differentiated from the mortality rate

### Mortality Rate
- proportion of the population that died from any cause during a specified time period
- crude mortality rate: unadjusted for age

### Basic Reproductive Number
- the average # of secondary infections that arise from one infection
- in a susceptible population

**Infection Control Precautions**
**Contact (impetigo, warts)**
- Wash hands
- Gloves
- Gown
- Wipe equipment after use

**Airborne (TB)**
- Contact precautions PLUS
- N95 mask (fit tested)
- Negative pressure room

**Droplet (influenza, mumps, pneumonia)**
- Contact precautions PLUS
- Goggles/face shield
- Surgical mask

Source: Public Health Ontario. http://www.publichealthontario.ca/en/eRepository/IPAC_Clinical_Office_Practice_2013.pdf http://www.oahpp.ca/resources/documents/pidac/Routine%20Practices%20and%20Additional%20Precautions.pdf

## Steps to Control an Outbreak

**Table 10. Ten-Step Approach**

| | Details |
|---|---|
| 1. Identify the investigation team and resources | Local public health units, e.g. Toronto Public Health |
| | Federal level, e.g. PHAC |
| 2. Establish existence of an outbreak | e.g. Receiving a report of a vomiting baseball team after a team dinner at a restaurant |
| 3. Verify the diagnosis | Obtain medical records and lab reports |
| | Conduct further clinical testing as needed |
| 4. Define a case | 3 components: Person, Place, Time |
| | e.g. "Diagnosis A: Person with XYZ signs and symptoms… Occurred after visiting X… During months/year" |
| 5. Find cases systemically and create a line listing | A line list should include clinical information (signs/symptoms, onset times/dates), demographic information, exposure information |
| 6. Perform descriptive epidemiology and develop hypotheses | Create epidemic curves (see Figure 16) |
| 7. Evaluate hypotheses and conduct additional studies as needed | Case-control studies: useful when not everyone exposed can be found and included in the study |
| | Cohort studies: useful when all persons exposed can be included in the study |
| 8. Implement control measures | Can occur at any stage in an outbreak |
| | e.g. Isolation |
| 9. Communicate findings | Involve the media to address public concerns and call for public action |
| 10. Continue surveillance | To determine when the outbreak is over |
| | Document the effectiveness of control measures |

Source: Adapted from Moore Z. Outbreak Investigations: The 10-Step Approach. Available at epi.publichealth.nc.gov/

For specific examples, see "Communicable Diseases" section in: Shah CP. Public Health and Preventive Medicine in Canada Toronto: Elsevier, 5th edition, 2003

**Active Surveillance**
Outreach such as visits or phone calls by the public health/surveillance authority to detect unreported cases (e.g. an infection control nurse goes to the ward and reviews temperature charts to see if any patient has a nosocomial infection)

**Passive Surveillance**
A surveillance system where the public health/surveillance authority depends on others to submit standardized forms or other means of reporting cases (e.g. ward staff notify infection control when new cases of nosocomial infections are discovered)

# Infection Control Targets

- interventions should target host, agent, environment, and their interactions

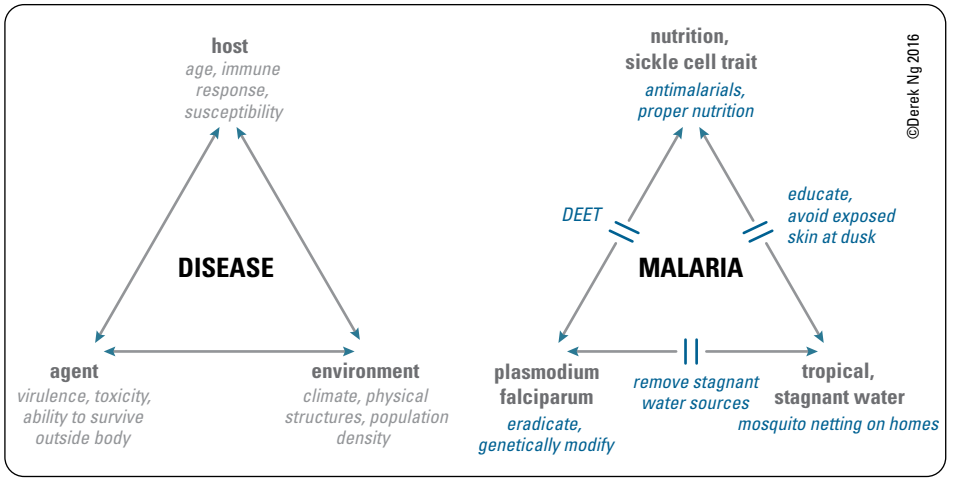



**Figure 16. Epidemiology triad as framework for infection control interventions: Practical example using malaria**

### The International Health Regulations (IHR)

- an international agreement involving 196 nations to prevent, protect against, control, and provide a public health response to pandemics
- a public health emergency of international concern (PHEIC) is "an extraordinary event which is determined to constitute a public health risk to other States through the international spread of disease and to potentially require a coordinated international response"
- the IHR Emergency Committee provides the WHO Director-General with temporary recommendations on PHEIC events

# Environmental Health

### Definition

- study of the association between environmental factors, both constructed and natural, and health
- environmental exposures
  - four common hazards: chemical, biological, physical, and radiation
  - four main reservoirs: air, food, water, and soil
  - three main routes: inhalation, ingestion, or absorption (skin)
- usually divided into two main settings:
  - workplace (including schools): may see high level exposure in healthy individuals (see *Occupational Health*, PH25)
  - non-workplace: lower levels of exposure over longer period of time. Affects vulnerable populations more severely, such as at extremes of age, immuno-suppressed. May be teratogenic
- health impacts of the environment also include factors such as urban planning and how individuals interact with the built environment (e.g. safe pedestrian and bicycle paths can facilitate more active lifestyles)

**Table 11. Environmental Health Jurisdiction**

| | |
|---|---|
| **Public Health Unit** | Enforcement of water and food safety regulations (including restaurant food safety)<br>Assessment of local environmental risks<br>Monitoring and follow-up of reportable diseases<br>Investigation of environmental contamination, clusters of disease |
| **Municipal Government** | Waste disposal, recycling, water and sewage treatment/collection/distribution |
| **Provincial and Territorial Government** | Water and air quality standards<br>Industrial emission regulation<br>Toxic waste disposal |
| **Federal Government** | Designating and regulating toxic substances<br>Regulating food products (e.g. Health Canada (drugs), CFIA)<br>Setting policy for pollutants that can travel across provincial boundaries |
| **International** | Multilateral agreements (e.g. Kyoto Protocol, UN Convention on Climate Change, International Joint Commission) |

### Source-Path-Receiver Model

- to prevent workplace injuries, strategies can be implemented to improve the safety profile of the source, modify the path, and/or protect the receiver

**Figure 17. Epidemic curves**

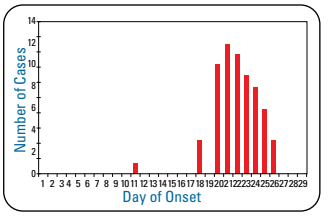



**Figure 17a. Point source epidemic curve**

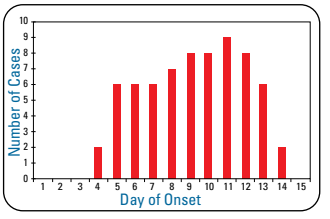



**Figure 17b. Extended continuous source epidemic curve**

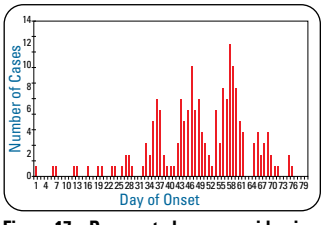



**Figure 17c. Propagated source epidemic curve**

**Environmental Health Jurisdiction - Taking an Environmental Health History**
CMAJ 2002 Apr 16;166(8):1049-1055

**$CH_2OPD_2$**
**C**ommunity
**H**ome
**H**obbies
**O**ccupation
**P**ersonal habits
**D**iet
**D**rugs

**BPA, The Toxin Concern of 2009**
Bisphenol A (BPA) is a chemical compound found in some hard, clear, lightweight plastics and resins. According to the NIH, animal studies suggest that ingested BPA may imitate estrogen and other hormones. In October 2008, Canada became the first country in the world to ban the import and sale of polycarbonate baby bottles containing BPA, stating that although exposure levels are below levels that cause negative effects, current safety margins need to be higher. The US FDA does not consider normal exposure to BPA to be a hazard, however the NIH has some concern that fetuses, infants, and children exposed to BPA may be at increased risk for early-onset puberty, prostate, and breast cancer

# Environmental Risk Assessment

### HIRA

### Hazard Identification
- what is the hazard involved?
- assess potential hazards by taking environmental health history

### Risk Characterization
- is the identified agent likely to elicit the patient's current symptoms?
- review known health impacts of the hazard and identify specific properties that contribute to or diminish adverse effects (e.g. evaluate threshold levels)

### Exposure Assessment
- is the patient's exposure to the environmental agent sufficient to have caused the current symptoms?
- quantify exposure through direct measurement or by reviewing frequency and nature of contact with hazard

Adapted from p.250, Sixth Edition of A Dictionary of Epidemiology by Miquel Porta

# Air

### Biological Hazards
- moulds thrive in moist areas; 10-15% of the population is allergic
- bacteria survive as spores and aerosols, can be distributed through ventilation systems (e.g. Legionella)
- dust mites (year-round) and pollens (seasonal) can trigger upper and lower-airway symptoms

### Chemical Hazards
- ground-level ozone
  - main component of smog with levels increasing in major cities
  - worsens asthma, irritates upper airway
- carbon monoxide (fossil fuel-related, common byproduct of combustion)
  - aggravates cardiac disease at low levels
  - headache, nausea, dizziness at moderate levels
  - fatal at high levels
- sulphur dioxide (fossil fuel-related), nitrogen oxides
  - contribute to acid rain and exacerbate breathing difficulties
- organic compounds at high levels (e.g. benzene, methylene chloride, tetrachloroethylene)
  - tend to be fat-soluble, easily absorbed through skin and difficult to excrete
- heavy metal emissions (e.g. nickel, cadmium, chromium)
  - variety of health effects: upper airway disease, asthma, decreased lung function
- second-hand tobacco smoke
  - respiratory problems, increase risk of lung cancer
  - particulates associated with decreased lung function, asthma, upper airway irritation

### Radiation Hazards
- sound waves
- ionizing radiation
  - radon is naturally produced by soil containing uranium or radium, can contaminate indoor air and is associated with ~20% of lung cancers
- ultraviolet radiation is increasing due to ozone layer destruction and increases risk of skin cancer
- non-ionizing radiation
  - visible light, infrared, microwave

# Water

### Biological Hazards
- mostly due to human and animal waste
- Indigenous Canadians, rural Canadians at higher risk
- bacteria: *Escherichia coli* (e.g. Walkerton, ON), *Salmonella, Pseudomonas, Shigella*
- protozoa: *Giardia, Cryptosporidium* (e.g. North Battleford, SK)

### Chemical/Industrial Hazards
- chlorination by-products (e.g. chlorinated water can cause cancer at high levels)
- volatile organic compounds, heavy metals, pesticides, and other industrial waste products can be present in groundwater
- mercury from fish (exposure during pregnancy can be neurotoxic for the fetus)
- asbestos (e.g. from old buildings)
- lead (can be found in paint, older buildings, and traditional medicines in dangerous quantities)

**Cannabis Legalization and Driving Under the Unfluence of Cannabis (DUIC)**
Source: Public Health Ontario. Evidence Brief-Driving Under the Influence of Cannabis, 2017
Since the Government of Canada stated its commitment to legalize cannabis via the Cannabis Act (Bill C-45) on April 13, 2017, the Canadian Task Force on Cannabis Legalization and Regulation specifically noted driving impairment as an important consideration. Higher cannabis use, cannabis-dependence, lower perceived risk from DUIC and normative beliefs about DUIC were identified as risk factors. As such, an act to amend the Criminal Code Bill C-46) was simultaneously introduced to enable the police the request an oral fluid sample for roadside drug screening and to implement THC per se whole blood limits (>2 ng/mL punishable). Public health was also advised to devise population-based interventions such as 6 hour waiting period recommendations before driving, as well as preventative strategies through addiction services, mass-media campaigns, and school-based instructional programs.

**Particulate Matter Air Pollution and Cardiovascular Disease: An Update to the Scientific Statement from the American Heart Association**
Circulation 2010 Jun 1;121(21):2331-78
A scientific statement by the American Heart Association in 2004 reported that exposure to particulate matter air pollution contributes to cardiovascular morbidity and mortality. An updated American Heart Association statement in 2010 confirmed a causal relationship between particulate matter exposure and cardiovascular morbidity and mortality. The statement reported that such an exposure over several hours to weeks may trigger cardiovascular disease-related mortality and non-fatal events, whereas longer exposures over several years may further increase cardiovascular mortality risk and reduce life expectancy within highly-exposed populations by several months to years.

**The Walkerton Tragedy**
In May 2000, the drinking water system in the town of Walkerton, ON, became contaminated with Escherichia coli O157:H7 and Campylobacter jejuni.
Over 2300 individuals became ill; 27 people developed hemolytic uremic syndrome and 7 individuals died in the outbreak.
Source: Ministry of the Attorney General. Report of the Walkerton inquiry. Ontario, 2002

**Water Fluoridation**
Water fluoridation, and the resulting decrease in dental caries and reduction in health inequities is one of the greatest public health achievements of the 20th century. At the recommended concentration of 0.7 mg/L, fluoride reduces cavities by 18-40%. Small but vocal groups opposed to fluoridation have claimed that fluoride intake is not easily controlled, and that children may be more susceptible to health problems. These claims have been widely debunked but still persist and have led to some communities opting not fluoridate their water, resulting in increased dental caries (eg: Calgary). Fluoride concentrations in municipal water should be 0.7 ppm

# Soil

## Biological Hazards
- biological contamination: tetanus, *Pseudomonas*

## Chemical Hazards
- contamination sources: rupture of underground storage tanks, use of pesticides and herbicides, percolation of contaminated water runoffs, leaching of wastes from landfills, dust from smelting and coal burning power plants, residue of industrial waste/development (e.g. urban agriculture), lead deposition, leakage of transformers
- most common chemicals: petroleum hydrocarbons, solvents, lead, pesticides, motor oil, other industrial waste products
- infants and toddlers at highest risk of exposure due to hand-mouth behaviours
- effects dependent on contaminant: leukemia, kidney damage, liver toxicity, neuromuscular blockade, developmental damage to the brain and nervous system, skin rash, eye irritation, headache, nausea, fatigue

# Food

## Biological Hazards

**Table 12. Comparison of Select Biological Contaminants of Food and Effects on Human Health**

| | Source | Effects |
|---|---|---|
| ***Salmonella*** | Raw eggs, poultry, meat | GI symptoms |
| ***Campylobacter*** | Raw poultry, raw milk | Joint pain, GI symptoms |
| ***Escherichia coli*** | Various including meat, sprouts<br>Primarily undercooked hamburger meat | Watery or bloody diarrhea<br>Hemolytic uremic syndrome (especially children) |
| ***Listeria monocytogenes*** | Unpasteurized cheeses, prepared salads, cold cuts | Listeriosis: nausea, vomiting, fever, headache, rarely meningitis or encephalitis |
| ***Clostridium botulinum*** | Unpasteurized honey, canned foods | Dizziness, weakness, respiratory failure<br>GI symptoms: thirst, nausea, constipation |
| **Prion (BSE*)** | Beef and beef products | Variant Creutzfeldt-Jakob disease |

*BSE = bovine spongiform encephalopathy

- other biological food contaminants include:
  - viruses, mould toxins (e.g. aflatoxin has been associated with liver cancer), parasites (e.g. *Toxoplasmi gondii*, tapeworm), paralytic shellfish poisoning (rare), genetically modified organisms (controversial as to health risks/benefits)

## Chemical Hazards
- many persistent organic pollutants are fat-soluble and undergo bioamplification
- drugs (antibiotics, hormones)
- inadequately prepared herbal medications
- food additives and preservatives
  - nitrites highest in cured meats; can be converted to carcinogenic nitrosamines
  - sulphites commonly used as preservatives; associated with sulphite allergy (hives, nausea, shock)
- pesticide residues
  - older pesticides (e.g. DDT) have considerable human health effects
- polychlorinated biphenyls (PCBs)
  - effects (severe acne, numbness, muscle spasm, bronchitis) much more likely to be seen in occupationally exposed individuals than in the general population
- dioxins and furans
  - levels highest in fish and marine mammals, also present in breast milk
  - can cause immunosuppression, liver disease, respiratory disease



**Organic Foods**
- Foods designated as "organic" in Canada must conform to the Organic Products Regulations enforced by the Canadian Food Inspection Agency
- Organic foods are not free of synthetic pesticide residues but typically contain smaller amounts compared to conventionally grown foods
- Currently, there has not been strong evidence to suggest that eating organic foods is safer or more nutritious compared to eating conventionally grown food

Source: Organic foods. Ann Intern Med 2012;157:348-66. Health Canada. Pesticides and food, 2011. UpToDate. Organic foods and children, 2009

# Occupational Health

- a field involved in the prevention of illness or injury and the promotion of health in the work environment
- services encompass recognizing and controlling exposure to hazards (primary prevention), occupational health surveillance and screening (secondary prevention) and treatment and rehabilitation (tertiary prevention)
- occupational disease often looks clinically the same as non-occupational disease, and without a thorough occupational health history may go unrecognized as distinct

## Taking an Occupational Health History

- current and previous duties at place of employment
- exposures
  - identification: screen for chemical, metal, dust, biological, and physical hazards as well as psychological stressors - workers may bring Safety Data Sheets (formerly MSDSs) that provide information about hazards of exposure
  - assessment: duration, concentration, route, exposure controls (e.g. ventilation and other environmental controls, personal protective equipment)
- temporal relationship: changes in symptoms in relationship to work environment, latency between first exposure and current symptoms
- presence of similar symptoms in co-workers
- non-work exposures to hazardous agents: home, neighbourhood, hobbies
- additional assessment may be required (e.g. chest radiography, ultrasound, PFT)



**Taking an Occupational Health Hx WHACS**
What do you do?
How do you do it?
Are you concerned about any particular exposures on or off the job?
Co-workers or others with similar problems?
Satisfied with your job?
J Occup Environ Med 1998;40:680-684

## Occupational Hazards

**Table 13. Occupational Hazards**

| Physical | Chemical | Biological | Psychosocial | Ergonomic / Safety |
|---|---|---|---|---|
| Noise (e.g. hearing loss)<br>Temperature<br>Heat cramps, heat exhaustion, heat stroke<br>Hypothermia, frostbite<br>Air pressure (barotrauma, decompression sickness)<br>Radiation<br>Non-ionizing: visible light, infrared<br>Ionizing: UV, x-rays, γ rays<br>Vibration-related disorders (secondary Raynaud's, whole body vibration) | Organic solvents (e.g. benzene, methyl alcohol; most toxic is carbon tetrachloride)<br>Mineral dusts (e.g. silica leads to silicosis and predisposition to TB, asbestos leads to diffuse fibrosis and mesothelioma, coal leads to pneumoconiosis)<br>Heavy metals (e.g. nickel, cadmium, mercury, lead)<br>Gases (e.g. halogen gases, sulphur dioxide, carbon monoxide, nitrogen oxides)<br>Second-hand smoke (causal factor for lung cancer, lung disease, heart disease, asthma exacerbations; may be linked to miscarriage)<br>Skin diseases (major portion of compensations, e.g. contact dermatitis, occupational acne, pigmentation disorders) | Exposure to bacteria, viruses, fungi, protozoa, Rickettsia<br>Exposure to biological proteins, endotoxins, enzymes, animal excreta<br>Blood should be considered a potentially toxic substance due to blood-borne infectious diseases (e.g. HIV, hepatitis B)<br>Consider exposure to disease in endemic countries, travellers from endemic countries, or recent travel history in the setting of acute onset of symptoms (e.g. malaria, SARS, TB) | Workload stressors<br>Responsibility<br>Fear of job loss<br>Geographical isolation<br>Shift work<br>Bullying<br>Harassment (sexual/non-sexual)<br>Incurs high cost from absenteeism, poor productivity, mental illness (e.g. post-traumatic stress disorder)<br>Workplace violence (involving staff, clients, the general public) | Ergonomic<br>Repetitive use/overuse injuries, excessive force, awkward postures, poorly designed physical work environment<br>Tenosynovitis, bursitis, carpal tunnel syndrome<br><br>Traumatic Injury Risks<br>Electrical contact<br>Slips, trips and falls, including falls from heights<br>Struck-by/pinning by equipment or objects<br>Contact with machinery/ moving parts<br>Fires and explosions |

## Workplace Legislation

- universal across Canada for corporate responsibility in the workplace: reasonable precautions to ensure a safe workplace, application of Workplace Hazardous Materials Information System (WHMIS), existence of joint health and safety committees in the workplace with representatives from workers and management
- jurisdiction in Canada is provincial (90% of Canadian workers), except for 16 federally regulated industries (e.g. airports, banks, highway transport) under the *Canada Labour Code*
- Ontario's *Occupational Health and Safety Act*
  - sets out rights of workers and duties of employers, procedures for workplace hazards, and law enforcement
  - workers have the right to:
    - know (e.g. be trained and have information about workplace hazards)
    - participate (e.g. have representatives on joint health and safety committees) refuse work (e.g. workers can decline tasks they feel are overly dangerous)
    - note: for some occupations, this right is restricted if, for example, danger/risk is normal part of work or refusal would endanger others (e.g. police, firefighters, some health care workers)



**Occupational Health Statistics**
- 1 in 68 employed workers in 2010 received workers compensation due to injury or harm on the job
- 4405 fatal work injuries in the United States in 2013; rate = 3.2/100,000 workers

Source: Employment and Social Development Canada. Work-related injuries, 2015
U.S. Bureau of Labour Statistics. Census of Fatal Occupational Injuries Charts, 1992-2013, 2014



Information about worker's compensation at: http://www.awcbc.org/en/index.asp

- stop work (e.g. 'certified' workers can halt work they feel is dangerous to other workers)
- enforced by Ministry of Labour via inspectors

- *Health Protection and Promotion Act* (HPPA) (Ontario)
  - Medical Officer of Health has right to investigate and manage health hazards where workplace exposures may impact non-workers (e.g. community members living close to the work site)

## Workplace Primary Prevention

- proactive efforts to reduce workplace illness or injury
- achieved through anticipating, recognizing, evaluating and controlling workplace hazards
- hierarchy of controls (see Figure 18) is followed to minimize exposure – elimination/substitution of hazards is most superior, followed by isolation (engineering controls), training and behavioural efforts (administrative controls), and lastly personal protective equipment

## Workplace Health Promotion

- a strategy for addressing the health and well-being of workers in the workplace, not legislated
- may include education, event planning, information campaigns, workplace supports to promote personal worker health and a healthy workforce

## Workplace Secondary Prevention

- for workers who are exposed to workplace hazards, goal is to identify earliest signs of overexposure or disease through medical surveillance (periodic examinations to identify early changes in a single worker or multiple workers). Some examples include:
  - whole blood lead testing to identify effectiveness of controls, need to remove workers from exposure
  - PFT for asthma (e.g. occupational dust exposure)
  - audiograms for hearing loss (e.g. occupational noise exposure)

## Workplace Tertiary Prevention

- treatment of the disease or injury to facilitate safe and timely return to the workforce
- may require rehabilitation, retraining, change in job duties, and/or workers' compensation (WSIB)
- often also involves accommodating the workplace for a worker who has a non-occupational injury or illness, with routine reassessments of the fit between the worker and their duties - work that is considered safety-sensitive may be restricted for workers with ailments that could impede their ability to work safely, or a worker may be medically determined to have limitations with what they can reasonably do at work
- advise relevant authorities if necessary (e.g. report notifiable diseases to public health, conditions impeding driving to Ministry of Transportation)

**Occupational Safety And Health Enforcement Tools For Preventing Occupational Diseases And Injuries**
Cochrane DB Syst Rev 2013:CD010183
**Objective**: To assess the effects of occupational safety and health regulation enforcement tools for preventing occupational diseases and injuries.
**Outcome**: Inspections decrease injuries in the long term, but not short term, with an unclear magnitude of effect.

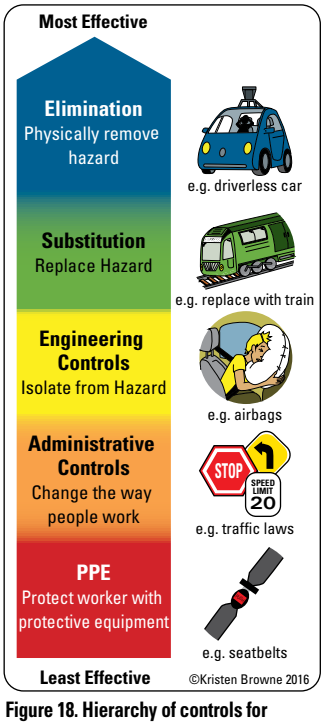



**Figure 18. Hierarchy of controls for reduction of occupational exposures**
Source: Modified from CDC. 2015. Hierarchy of controls. http://www.cdc.gov/niosh/topics/hierarchy/

# Appendix – Mandatory Reporting

## Reportable Diseases

As an essential part of the public health system, physicians in Canada are required by provincial law to report certain diseases to public health. Physician reporting is also outlined by provincial physician licensing Colleges (e.g. College of Physicians and Surgeons of Ontario (CPSO)). Failure to report can result in suspension of a license to practice.

The reasons that reporting is mandatory include:

1. to identify and control an outbreak
2. to prevent spread if the disease presents a significant threat to individuals or a subset of the population (e.g. Lassa Fever)
3. if the disease is preventable with immunization (e.g. polio, diphtheria, congenital rubella)
4. if infected individuals require education, treatment, and/or partner notification (e.g. gonorrhea, TB)
5. surveillance (to monitor disease trends over time)

***Ontario's Workplace Safety and Insurance Act*** (Each province will have their own similar legislation)

- Establishes Workplace Safety and Insurance Board (WSIB), an autonomous government agency that oversees workplace safety training and administers insurance for workers and employers
- WSIB decides benefits for workers, which may include reimbursement for
  - Loss of earned income
  - Non-economic loss (e.g. physical, functional, or psychological loss extending beyond the workplace)
  - Loss of retirement income
  - Health care expenses (e.g. first-aid, medical treatment)
  - Survivor benefits (e.g. dependents and spouses can receive benefits)
- Employers pay for costs (e.g. no government funding)
- No-fault insurance (e.g. worker has no right to sue the employer) in return for guaranteed compensation for accepted claims
- Negligence is not considered a factor
- Physicians are required to provide the WSIB with information about a worker's health without a medical waiver once a claim is made

For more information: http://www.wsib.on.ca/en/community/WSIB

The list of Reportable Diseases is now called "Diseases of Public Health Significance 2018. Each province will have a similar legislation
Note: Diseases marked * (and Influenza in institutions) should be reported immediately to the Medical Officer of Health by either telephone (24 hours a day, 7 days a week) or fax (Mon-Fri, 8:30 am – 4:30 pm only). Other diseases can be reported the next working day by fax, phone or mail.
Source: Health Protection and Promotion Act, O. Reg. 559/91, amended to O. Reg.49/07 (update)

Acquired Immunodeficiency Syndrome (AIDS)
Acute flaccid paralysis <15 yr
Amoebiasis
Anthrax*

Botulism*
Brucellosis*

Campylobacter enteritis
Chancroid
Chickenpox (Varicella)
Chlamydia trachomatis infections
Cholera*
Clostridium difficile* associated disease (CDAD) outbreaks in public hospitals
Creutzfeldt-Jakob Disease, all types
Cryptosporidiosis*
Cyclosporiasis*

Diphtheria*

Encephalitis*, including:
1. Primary, viral*
2. Post-infectious
3. Vaccine-related
4. Subacute sclerosing panencephalitis
5. Unspecified

Food poisoning, all causes*

Gastroenteritis, institutional outbreaks*
Giardiasis, except asymptomatic cases*
Gonorrhea

Haemophilus influenzae b disease, invasive*
Hantavirus pulmonary syndrome*

Hemorrhagic fevers*, including:
1. Ebola virus disease*
2. Marburg virus disease*
3. Other viral causes*

Hepatitis, viral*:
1. Hepatitis A*
2. Hepatitis B
3. Hepatitis C

Influenza
(Note: Influenza in institutions*)

Lassa Fever*
Legionellosis*
Leprosy
Listeriosis*
Lyme Disease

Malaria
Measles*
Meningitis, acute*:
1. Bacterial*
2. Viral*
3. Other*

Meningococcal disease, invasive*
Mumps

Ophthalmia neonatorum

Paralytic shellfish poisoning
Paratyphoid fever*
Pertussis (whooping cough)
Plague*

Pneumococcal disease, invasive
Poliomyelitis, acute*

Psittacosis/Ornithosis

Q Fever*

Rabies*
Respiratory infection outbreaks in institutions*
Rubella*
Rubella, congenital syndrome

Salmonellosis
Severe Acute Respiratory Syndrome (SARS)*
Shigellosis*
Smallpox*
Streptococcal infections, Group A invasive*
Streptococcal infections, Group B neonatal
Syphilis

Tetanus
Trichinosis
Tuberculosis, active and latent
Tularemia*
Typhoid Fever*

Verotoxin-producing E. coli infection* indicator conditions, including Hemolytic Uremic Syndrome (HUS)*

West Nile Virus illness*, including:
1. West Nile fever*
2. West Nile neurological manifestations *

Yellow Fever*
Yersiniosis

# Other Reportable Conditions

- in addition to reporting diseases, physicians have a legal responsibility to report certain conditions. The list below highlights some reportable conditions for Ontario, but is not exhaustive. See your jurisdiction's regulatory body for the full list

### Live Births, Stillbirths, and Deaths – to the Registrar General or Coroner*
- all live and stillbirths must be reported within 2 business days
- a physician with sufficient familiarity of a patient's illness or was in attendance of a deceased patient's last illness must complete and sign the medical certificate of death
- physicians must contact a coroner or the police if patient is suspected to have deceased from violence, misadventure, negligence, misconduct or malpractice or any cause other than disease; by unfair means; during pregnancy or postpartum from circumstances reasonably attributed to the pregnancy; suddenly and unexpectedly; from an illness not treated by a legally qualified medical practitioner; or under circumstances that may require investigation*
- physicians must report all medically assisted deaths to the coroner*

### Child Abuse – to Local Children's Aid Society (CAS)
- all child abuse and neglect where reasonable grounds to suspect exist (including physical harm, emotional harm, sexual harm, and neglect)
- duty to report is ongoing: if additional reasonable grounds are suspect, a further report to CAS is necessary

### Gunshots Wounds – to Local Police Service
- all patients with a gunshot or stab wounds
- self-inflicted knife wounds are not reportable

### Abuse of Long-Term Care or Retirement Home Residents – to the Registrar of the Retirement Homes Regulatory Authority or Long-Term Care Home Director
- any resident suspected of being subject to or at risk of improper or incompetent treatment or care, abuse or neglect, or unlawful conduct including financial abuse

### Unfit to Drive – to Provincial Ministry of Transportation
- all patients with a medical condition (e.g. dementia, untreated epilepsy) that may impede their driving ability
- if a physician does not report and the driver gets into an accident, the physician may be held liable

### Unfit to Fly – to Federal Ministry of Transportation
- all patients believed to be flight crew members or air traffic controller with a medical or optometric condition that is likely to constitute a hazard to aviation safety

Source: CPSO. Mandatory and Permissive Reporting. 2012. Available from: http://www.cpso.on.ca/policies-publications/policy/mandatory-and-permissive-reporting

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# R Respirology

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# Acronyms

| | |
|---|---|
| A-a | alveolar-arterial |
| A-a$DO_2$ | alveolar-arterial oxygen diffusion gradient |
| ABG | arterial blood gas |
| ACEI | angiotensin converting enzyme inhibitor |
| ACV | assist-control ventilation |
| AECOPD | acute exacerbation of COPD |
| AFB | acid-fast bacillus |
| AFP | alpha-fetoprotein |
| AFOP pneumonia | acute fibrinous and organizing |
| AHI | apnea hypopnea index |
| AIP | acute interstitial pneumonia |
| ALI | acute lung injury |
| ALS | amyotrophic lateral sclerosis |
| ANA | antinuclear antibody |
| ANCA | anti-neutrophil cytoplasmic antibody |
| APTT | activated partial thromboplastin time |
| ARDS | acute respiratory distress syndrome |
| ARMS | artificial rupture of membranes |
| ASA | acetylsalicylic acid (Aspirin®) |
| ASD | atrial septal defect |
| AV | arteriovenous |
| AVM | arteriovenous malformation |
| AVN | avascular necrosis |
| BG | blood glucose |
| BiPAP | bilevel positive airway pressure |
| BOOP | bronchiolitis obliterans with organizing pneumonia |
| BSA | body surface area |
| CA | cancer |
| CABG | coronary artery bypass grafting |
| CCB | calcium channel blocker |
| CD | Crohn's disease |
| CF | cystic fibrosis |
| CHF | congestive heart failure |
| CI | cardiac index |
| CO | cardiac output |
| COP | cryptogenic organizing pneumonia |
| COPD | chronic obstructive pulmonary disease |
| CPAP | continuous positive airway pressure |
| CSA | central sleep apnea |
| CTEPH | chronic thromboembolic pulmonary hypertension |
| CVD | cardiovascular disease |
| CVP | central venous pressure |
| CWP | coal worker's pneumoconiosis |
| DIC | disseminated intravascular coagulation |
| DIP | desquamative interstitial pneumonia |
| $DL_{CO}$ | carbon monoxide diffusing capacity of lung |
| DM | diabetes mellitus |
| DOAC | direct oral anticoagulant |
| EBUS | endobronchial ultrasound |
| ECMO | extracorporeal membrane oxygenation |
| EGPA | eosinophilic granulomatosis with polyangiitis |
| EGDT | early goal-directed therapy |
| ERV | expiratory reserve volume |
| ETT | endotracheal tube |
| FEF | forced expiratory flow rate |
| $FEV_1$ | forced expiratory volume in 1 second |
| $FiO_2$ | fraction of oxygen in inspired air |
| FRC | functional residual capacity |
| GBM | glomerular basement membrane |
| GERD | gastroesophageal reflux disease |
| GPA | granulomatosis with polyangiitis |
| H/A | headache |
| HPA | hypothalamic-pituitary axis |
| HRT | hormone replacement therapy |
| IBD | inflammatory bowel disease |
| IC | inspiratory capacity |
| ICP | intracranial pressure |
| ICS | inhaled corticosteroid |
| ILD | interstitial lung disease |
| IPF | idiopathic pulmonary fibrosis |
| IPPFE | idiopathic pleuroparenchymal fibroelastosis |
| LAAC | long-acting anti-cholinergic |
| LABA | long-acting beta-agonist |
| LIP | lymphocytic interstitial pneumonia |
| LLN | lower limit of normal |
| LMWH | low molecular weight heparin |
| LTRA | leukotriene receptor antagonist |
| LV | left ventricle |
| LVEDP | left ventricular end diastolic pressure |
| LVF | left ventricular failure |
| MAC | *Mycobacterium avium* complex |
| MDI | metered dose inhaler |
| MEP | maximum expiratory pressure |
| MIP | maximum inspiratory pressure |
| MSA | mixed sleep apnea |
| MSK | musculoskeletal |
| NPPV | non-invasive positive pressure ventilation |
| NSCLC | non-small cell lung cancer |
| NSIP | non-specific interstitial pneumonia |
| NTT | nasotracheal tube |
| N/V | nausea/vomiting |
| OCP | oral contraceptive pill |
| OSA | obstructive sleep apnea |
| PA | posteroanterior |
| $P_aCO_2$ | arterial partial pressure of carbon dioxide |
| $P_aO_2$ | arterial partial pressure of oxygen |
| $P_AO_2$ | alveolar partial pressure of oxygen |
| $P_{atm}$ | atmospheric pressure |
| PCP | *Pneumocystis carinii* pneumonia |
| PCV | pressure control ventilation |
| PCWP | pulmonary capillary wedge pressure |
| PDA | patent ductus arteriosus |
| PE | pulmonary embolism |
| PEEP | positive end expiratory pressure |
| PEF | peak expiratory flow |
| PFT | pulmonary function tests |
| PMNs | polymorphonuclear cells |
| PP | pulse pressure |
| PSV | pressure support ventilation |
| PTH | parathyroid hormone |
| PTT | partial thromboplastin time |
| PUD | peptic ulcer disease |
| PVC | premature ventricular contraction |
| RA | rheumatoid arthritis |
| RAD | right axis deviation |
| RAP | right atrial pressure |
| RBBB | right bundle branch block |
| RF | rheumatoid factor |
| RV | residual volume |
| RVEDV | right ventricular end diastolic volume |
| RVH | right ventricular hypertrophy |
| RVSP | right ventricular systolic pressure |
| SCC | squamous cell carcinoma |
| SCLC | small cell lung cancer |
| $S_{cv}O_2$ | central venous oxygen saturation |
| SIMV | synchronous intermittent mandatory ventilation |
| SIRS | systemic inflammatory response syndrome |
| SOFA | sepsis-related organ failure assessment score |
| qSOFA | quick sepsis-related organ failure assessment score |
| SV | stroke volume |
| SVC | superior vena cava |
| SVRI | systemic vascular resistance index |
| TB | tuberculosis |
| TCA | tricyclic antidepressant |
| TLC | total lung capacity |
| TNM | tumour, node, metastasis |
| TPN | total parenteral nutrition |
| UC | ulcerative colitis |
| UIP | usual interstitial pneumonia |
| URTI | upper respiratory tract infection |
| V/Q | ventilation-to-perfusion |
| VATS | video-assisted thoracoscopic surgery |
| VC | vital capacity |
| VSD | ventricular septal defect |
| VTE | venous thromboembolism |
| $V_T$ | tidal volume |

# Approach to the Respiratory Patient

## Basic Anatomy Review

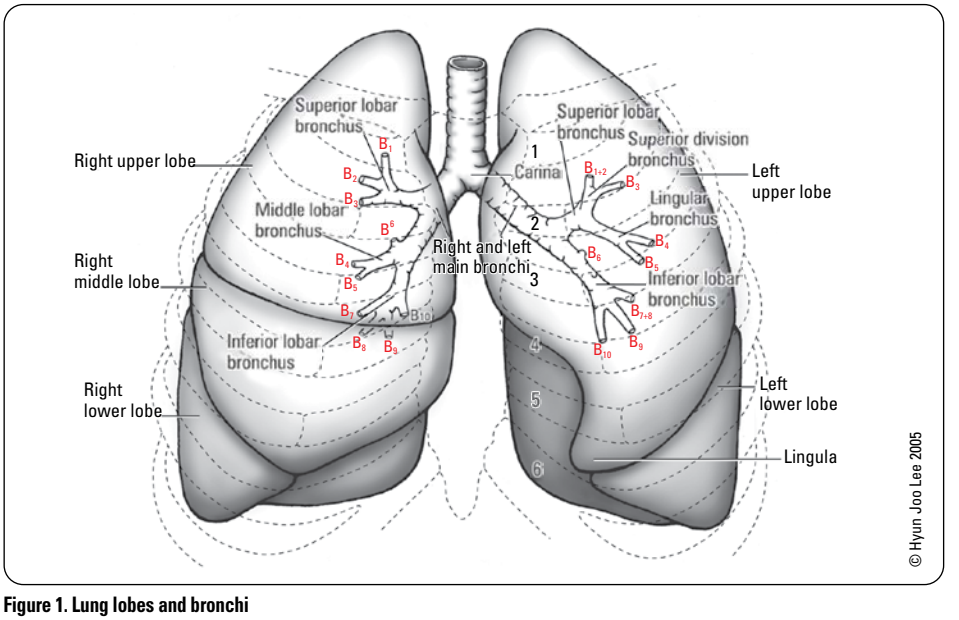



**Figure 1. Lung lobes and bronchi**

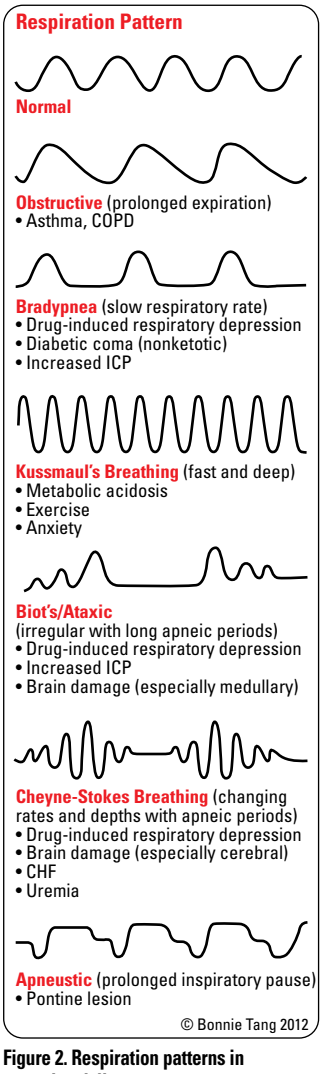



**Figure 2. Respiration patterns in normal and disease states**

# Differential Diagnoses of Common Presentations

## Table 1. Differential Diagnosis of Dyspnea

| ACUTE DYSPNEA (MINUTES-DAYS) |
|---|
| **Cardiac** |
| Acute myocardial infarction |
| CHF exacerbation |
| Cardiac tamponade |
| Coronary artery disease |
| Arrhythmia |
| **Pulmonary** |
| Upper airway obstruction (anaphylaxis, aspiration, croup, EBV) |
| Airway disease (asthma, COPD exacerbation, bronchitis) |
| Parenchymal lung disease (ARDS, pneumonia) |
| Pulmonary vascular disease (PE, vasculitis) |
| Pleural disease (pneumothorax, tension pneumothorax) |
| **Neurologic/Psychogenic** |
| Respiratory control (metabolic acidosis, trauma) |
| Anxiety |
| Panic attack |
| **CHRONIC DYSPNEA (+4 WEEKS)** |
| **Cardiac** |
| Valvular heart disease |
| Myocardial dysfunction (decreased CO) |
| **Pulmonary** |
| Airway disease (asthma, COPD) |
| Parenchymal lung disease (interstitial disease) |
| Pulmonary vascular disease (pulmonary HTN, vasculitis) |
| Pleural disease (effusion) |
| **Metabolic** |
| Medication |
| Severe anemia |
| Hyperthyroidism |
| **Neuromuscular and chest wall disorders** |
| Deconditioning, obesity, pregnancy, neuromuscular disease |
| **Psychogenic** |
| Anxiety |

## Table 2. Differential Diagnosis of Chest Pain

| NONPLEURITIC | PLEURITIC |
|---|---|
| **Pulmonary** | **Pulmonary** |
| Pneumonia | Pneumonia |
| PE | PE |
| Neoplasm | Neoplasm |
| **Cardiac** | Pneumothorax |
| MI | Pleurisy |
| Myocarditis/pericarditis | Hemothorax |
| Deconditioning | TB |
| **Esophageal** | Empyema |
| GERD | **Cardiac** |
| Spasm | Pericarditis |
| Esophagitis | Dressler's syndrome |
| Ulceration | **GI** |
| Achalasia | Subphrenic abscess |
| Neoplasm | **MSK** |
| Esophageal rupture | Costochondritis |
| **Mediastinal** | Fractured rib/flail chest |
| Lymphoma | Myositis |
| Thymoma | Herpes zoster |
| **Subdiaphragmatic** | **Psych** |
| PUD | Anxiety |
| Gastritis | Panic attack/disorder |
| Biliary colic | |
| Pancreatitis | |
| **Vascular** | |
| Aortic aneurysm | |
| Aortic dissection | |
| Aortic injury/rupture | |
| **MSK** | |
| Costochondritis | |
| Skin | |
| Breast | |
| Ribs | |
| Rheumatic disease | |
| **Metabolic** | |
| Anemia | |
| Hyperthyroidism | |
| **Psych** | |
| Anxiety | |
| Panic attack/disorder | |
| **Miscellaneous** | |
| Pregnancy | |
| Weight gain | |

(see Cardiology and Cardiac Surgery C4 and Emergency Medicine ER21)

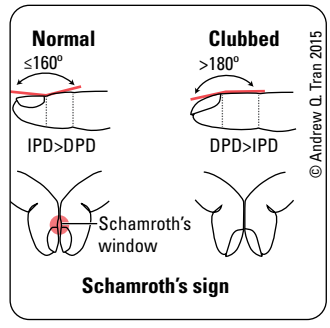



**Figure 3. Signs of nail clubbing**

**Signs of Respiratory Distress**
- Tachypnea
- Central/peripheral cyanosis
- Tachycardia
- Inability to speak
- Nasal flaring
- Tracheal tug
- Intercostal indrawing
- Tripoding
- Abdominal breathing (paradoxical breathing)

**Common Causes of Clubbing**
- Pulmonary: Lung CA, bronchiectasis, pulmonary fibrosis, abscess, CF, TB, empyema, A-V fistula/malformation (NOT COPD)
- Cardiac: Cyanotic congenital heart disease, endocarditis
- GI: IBD, celiac, cirrhosis, neoplasm
- Endocrine: Graves' disease
- Other: Other malignancy, primary hypertrophic osteoarthropathy

Clubbing is not seen in COPD – if present, think malignancy

**Hemoptysis**
- Most common cause is bronchitis
- 90% of massive hemoptysis is from the bronchial arteries
- Considered "massive" if >600 mL/24 h or bleeding rate of >100 mL/h

**Most Common Causes of Chronic Cough in the Non-smoking Patient (cough >3 mo with normal CXR)**
- GERD
- Asthma
- Postnasal drip
- ACEI

## Table 3. Differential Diagnosis of Hemoptysis

| AIRWAY DISEASE |
|---|
| **Acute or chronic bronchitis*** |
| Bronchiectasis |
| Bronchogenic CA |
| Bronchial carcinoid tumour |
| Cystic Fibrosis |
| **Parenchymal Disease** |
| Pneumonia |
| TB |
| Lung abscess |
| Fungal infection |
| Primary lung cancer |
| Pulmonary metastasis |
| **Vascular Disease** |
| PE |
| Elevated pulmonary venous pressure: |
| Left ventricular dysfunction/failure |
| Mitral stenosis |
| Vascular malformation |
| Vasculitis |
| Goodpasture's syndrome |
| Idiopathic pulmonary hemosiderosis |
| **Miscellaneous** |
| Impaired coagulation |
| Pulmonary endometriosis |
| Trauma |
| Foreign Body |

*Most common cause of hemoptysis

## Table 4. Differential Diagnosis of Cough

| AIRWAY IRRITANTS |
|---|
| Inhaled smoke, dusts, fumes |
| Postnasal drip (upper airway cough syndrome) |
| Aspiration |
| **Gastric contents (GERD)*** |
| Oral secretions |
| Foreign body |
| **Airway Disease** |
| **URTI including postnasal drip and sinusitis*** |
| Acute or chronic bronchitis |
| Bronchiectasis |
| Neoplasm |
| External compression by node or mass lesion |
| **Asthma*** |
| COPD |
| **Parenchymal Disease** |
| Pneumonia |
| Lung abscess |
| Interstitial lung disease |
| **PE** |
| **CHF** |
| **Drug-induced (e.g. ACEI)** |
| **Smoking** |

*"Big Three" causes of chronic cough

Adapted from: Weinberger SE. Principles of pulmonary medicine, 5th ed. 2008. With permission from Elsevier

# Pulmonary Function Tests

- useful in differentiating the pattern of lung disease (obstructive vs. restrictive)
- assess lung volumes, flow rates, and diffusion capacity
- **note:** normal values for $FEV_1$ are approximately ±20% of the predicted values (for age, sex, and height); ethnicity may affect predicted values

**Table 5. Comparison of Lung Flow and Volume Parameters in Lung Disease**

| | Obstructive | Restrictive |
|---|---|---|
| | Decreased flow rates (most marked during expiration) | Decreased lung compliance |
| | Air trapping (increased RV/TLC) | Decreased lung volumes |
| | Hyperinflation (increased FRC, TLC) | |
| **DDx** | Asthma, COPD, CF, bronchiolitis, bronchiectasis* | ILD, pleural disease, neuromuscular disease, chest wall disease |
| **$FEV_1$/FVC** | ↓ | ↑ or N |
| **TLC** | ↑ or N | ↓ |
| **RV** | ↑ or N | ↓ |
| **RV/TLC** | ↑ or N | N |
| **$DL_{CO}$** | ↓/↑ or N | ↓ or N |

*Bronchiectasis can be obstructive or mixed

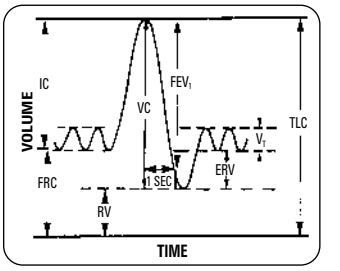



**Figure 4A. Lung volumes and capacities**

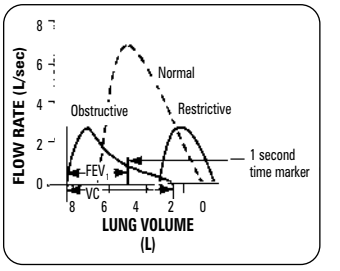



**Figure 4B. Expiratory flow volume curves**
Adapted with permission from Elsevier. Weinberger SE. Principles of pulmonary medicine, 5th ed. 2008

**Table 6. Common Respirology Procedures**

| Technique | Purpose | Description |
|---|---|---|
| **Plethysmography ("body box")** | Measure FRC | After a normal expiration the patient inhales against a closed mouthpiece<br>Resultant changes in the volume and pressure of the plethysmograph are used to calculate the volume of gas in the thorax<br>Useful for patients with air trapping |
| **He Dilution** | Measure FRC | A patient breathes from a closed circuit containing a known concentration and volume of helium<br>Since the amount of helium remains constant, FRC is determined based on the final concentration of the helium in the closed system<br>Only includes airspaces that communicate with the bronchial tree |
| **Bronchoscopy** | Diagnosis and therapy | A flexible or rigid bronchoscope is used for visualization of a patient's airways allows for:<br>Bronchial and broncho-alveolar lavage (washings) for culture and cytology<br>Endobronchial or transbronchial tissue biopsies<br>Removal of secretions/foreign bodies/blood<br>Laser resections<br>Airway stenting<br>Mediastinal lymph nodes can also be sampled using a special bronchoscope equipped with an U/S probe (EBUS) |

**Lung Volumes**
ERV – Expiratory Reserve Volume
FEF – Forced Expiratory Flow Rate
$FEV_1$ – Forced Expiratory Volume (in one second)
FRC – Functional Residual Capacity
IC – Inspiratory Capacity
RV – Residual Volume
TLC – Total Lung Capacity
VC – Vital Capacity
$V_T$ – Tidal Volume

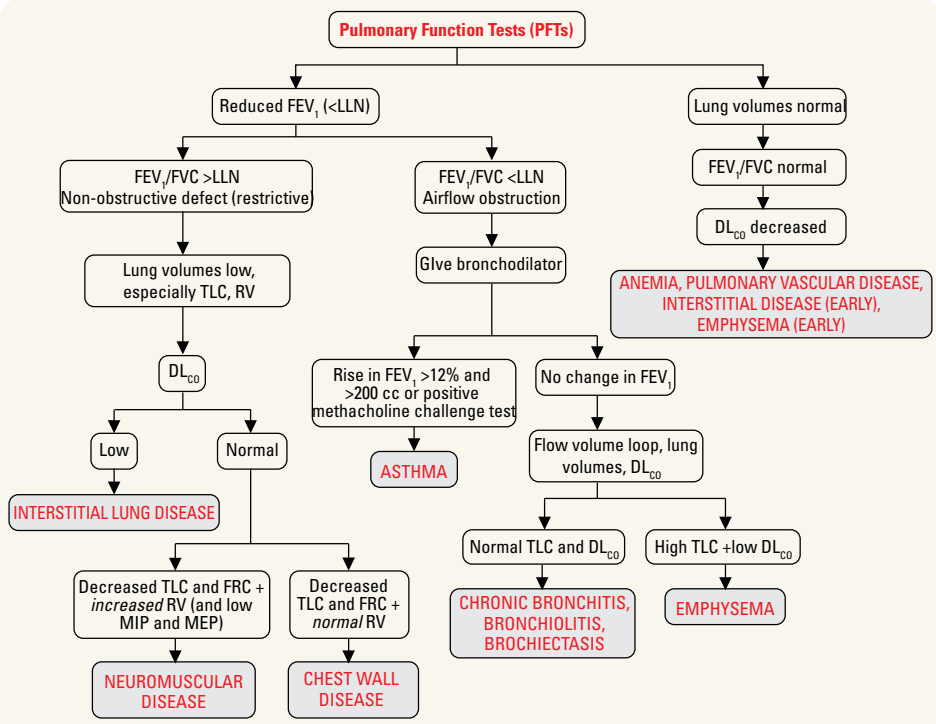



**Figure 5. Interpreting PFTs**

# Chest X-Rays

- see Medical Imaging, MI2

**Table 7. CXR Patterns and Differential Diagnosis**

| Pattern | Signs | Common DDx |
|---|---|---|
| **Consolidation ("Airspace disease")** | Air bronchogram<br>Silhouette sign<br>Less visible blood vessels | Acute: water (PE), pus (pneumonia), blood (hemorrhage)<br>Chronic: neoplasm (lymphoma), inflammatory (eosinophilic pneumonia), infection (TB, fungal) |
| **Reticular ("Interstitial disease")** | Increased linear markings<br>Fine or ground glass<br>Honeycombing (end stage IPF) | ILD (IPF, collagen vascular disease, asbestos, drugs), hypersensitivity pneumonitis, asbestosis, collagen vascular disease, drug reactions |
| **Nodular** | Cavitary vs. non-cavitary | Cavitary: neoplasm (primary vs. metastatic lung cancer), infectious (anaerobic or Gram negative, TB, fungal), inflammatory (RA, sarcoidosis, granulomatosis with polyangiitis [GPA]), IPF<br>Non-cavitary: above + sarcoidosis, Kaposi's sarcoma (in HIV), silicosis and other pneumoconioses |

# Arterial Blood Gases

- provides information on acid-base and oxygenation status
- see Nephrology, NP16

## Approach to Acid-Base Status

1. Is the pH acidemic (pH <7.35), alkalemic (pH >7.45), or normal (pH 7.35-7.45)?
2. What is the primary disturbance?
   - metabolic: change in $HCO_3^-$ and pH in same direction
   - respiratory: change in $HCO_3^-$ and pH in opposite directions
3. Is there appropriate compensation? (see Table 8)
   - metabolic compensation occurs over 2-3 d reflecting altered renal $HCO_3^-$ production and excretion
   - respiratory compensation through ventilatory control of $P_aCO_2$ occurs immediately
   - inadequate compensation may indicate a second acid-base disorder

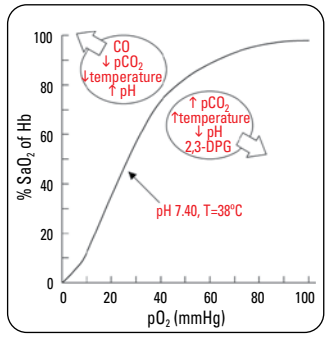



**Figure 6. Oxygen-Hb dissociation curve**

**Table 8. Expected Compensation for Specific Acid-Base Disorders**

| Disturbance | $P_aCO_2$ (mmHg) (normal ~40) | $HCO_3^-$ (mmHg) (normal ~24) |
|---|---|---|
| **Respiratory Acidosis** | | |
| Acute | ↑ 10 | ↑ 1 |
| Chronic | ↑ 10 | ↑ 3 |
| **Respiratory Alkalosis** | | |
| Acute | ↓ 10 | ↓ 2 |
| Chronic | ↓ 10 | ↓ 5 |
| **Metabolic Acidosis** | ↓ 1 | ↓ 1 |
| **Metabolic Alkalosis** | ↑ 5-7 | ↑ 10 |

4. if there is metabolic acidosis, what is the anion gap and osmolar gap?
   - anion gap = $[Na^+]-([Cl^-]+[HCO_3^-])$; normal 5-14 mmol/L
   - osmolar gap = measured osmolarity – calculated osmolarity = measured – $(2[Na^+]$ + glucose + urea); normal ≤10 mmol/L
     - abnormal osmolar gap indicates the presence of alcohols
5. if anion gap is increased, is the change in bicarbonate the same as the change in anion gap?
   - if not, consider a mixed metabolic picture

**Table 9. Differential Diagnosis of Respiratory Acidosis**

*Increased $P_aCO_2$ secondary to hypoventilation*

| Respiratory Centre Depression (Decreased RR) | Neuromuscular Disorders (Decreased Vital Capacity) | Lung Disease | Mechanical Hypoventilation (Inadequate Mechanical Ventilation) |
|---|---|---|---|
| Drugs (anesthesia, sedatives, narcotics) | Myasthenia gravis | COPD | |
| Trauma | Guillain-Barré syndrome | Asthma | |
| Encephalitis | Botulism | Pulmonary edema | |
| Stroke | Poliomyelitis | Pneumothorax | |
| Central apnea | Muscular dystrophies | Pneumonia | |
| Supplemental $O_2$ in chronic $CO_2$ retainers (e.g. COPD) | ALS | ILD (late stage) | |
| | Myopathies | ARDS | |
| | Chest wall disease (obesity, kyphoscoliosis) | | |

**Table 10. Differential Diagnosis of Respiratory Alkalosis**

*Decreased $P_aCO_2$ secondary to hyperventilation*

| | Respiratory Centre Stimulation | Mechanical Hyperventilation (Excessive Mechanical Ventilation) |
|---|---|---|
| Pulmonary disease (pneumonia, edema, PE, interstitial fibrosis) | Drugs (ASA, progesterone, theophylline, catecholamines, psychotropics, nicotine, salicylates) | |
| Severe anemia | Chest wall disease (obesity, kyphoscoliosis) | |
| Heart failure | Hepatic failure | |
| High altitude | Gram-negative sepsis | |
| | Pregnancy | |
| | Anxiety | |
| | Pain | |

- see Nephrology, NP16 for differential diagnosis of metabolic acidosis and alkalosis

**Factors that Shift the Oxygen-Hb Dissociation Curve to the Right**

**"CADET, face right!"**
**C**$O_2$
**A**cid
2,3-**D**PG
**E**xercise
**T**emperature (increased)

Note: 2,3-DPG (2,3-diphosphoglycerate) is now called 2,3-BPG (2,3-biphosphoglycerate)

Acidosis ⟷ Hyperkalemia
Alkalosis ⟷ Hypokalemia

Note: Mixed acid-base disturbances can still have a "normal" pH

Osmolar Gap = measured osmolarity – calculated osmolarity; for calculated osmolarity think "2 salts and a sticky BUN" (2Na + glucose + urea)

**Anion Gap Metabolic Acidosis**

**MUDPILESCAT**
**M**ethanol
**U**remia
**D**iabetic ketoacidosis/starvation ketoacidosis
**P**henformin/**P**araldehyde
**I**soniazid, **I**ron, **I**buprofen
**L**actic acidosis
**E**thylene glycol
**S**alicylates
**C**yanide, **C**arbon dioxide
**A**lcoholic ketoacidosis
**T**oluene, **T**heophylline

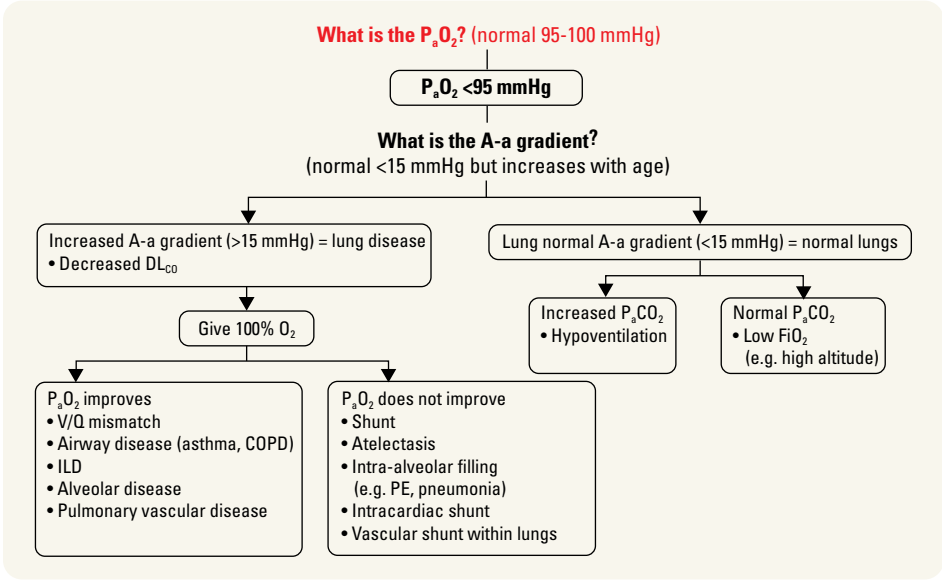



**Figure 7. Approach to hypoxemia**

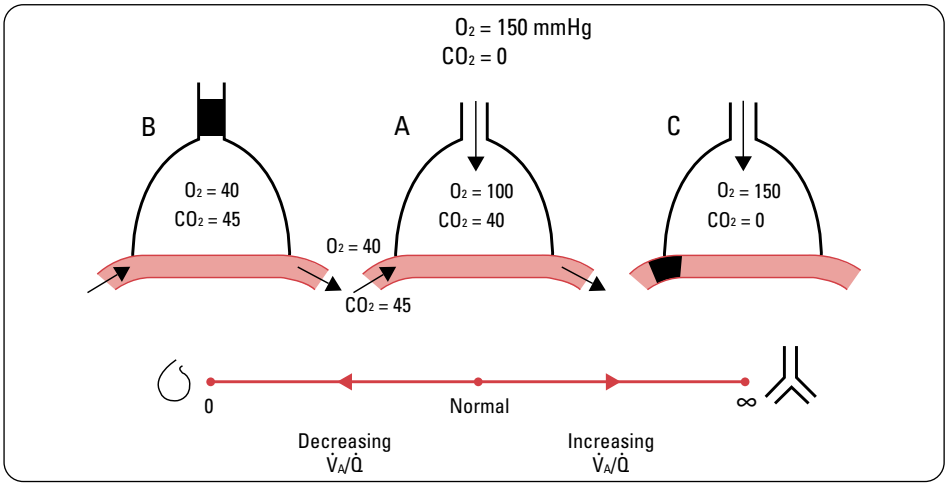



**Figure 8. Pathophysiology of V/Q mismatch**

Figure adapted from West – Respiratory Physiology: The Essentials. 9th Ed. 2012. Lippincott Williams & Wilkins, Philadelphia, PA.

**At Sea Level on Room Air**
$FiO_2$ = 0.21
$P_{atm}$ = 760 mmHg
$PH_2O$ = 47 mmHg
RQ = 0.8
Thus, A-a$DO_2$ Gradient on Room Air
A-a$DO_2$ = (150 – 1.25 [$P_aCO_2$]) – $P_aO_2$

**Diffusion Capacity for CO**

**$DL_{CO}$ decreases in:**
- Interstitial lung disease
- Pulmonary vascular disease
- Anemia
- Emphysema (decreased surface area)

**$DL_{CO}$ increases in/with:**
- Asthma
- Obesity
- Pulmonary hemorrhage
- Left-to-right intracardiac shunt
- Polycythemia
- Postexercise physiology (increased pulmonary blood volume)

**Pulmonary Shunt**
Occurs when the capillary networks of the alveoli are perfused, yet there is a lack of adequate ventilation (and thus oxygenation) in that alveolus or group of alveoli. Thus this blood enters the pulmonary venous system without being oxygenated

# Airway Disease

## Pneumonia

- see Infectious Diseases, ID7

## Asthma

- see Family Medicine, FM16 and Pediatrics, P81

### Definition
- chronic inflammatory disorder of the airways resulting in episodes of reversible bronchospasm causing airflow obstruction
- associated with reversible airflow limitation and airway hyper-responsiveness to endogenous or exogenous stimuli
- inflamed airways undergo a variety of changes including hypertrophied smooth airway muscles and mucous producing goblet cells

### Epidemiology
- common, 7-10% of adults, 10-15% of children
- most children with asthma significantly improve in adolescence
- often family history of atopy (asthma, allergic rhinitis, eczema)
- occupational asthma (organic allergies, isocyanates, animals, etc.)

**Airway Obstruction (decreased $FEV_1$)**
- Asthma
- COPD (chronic bronchitis, emphysema)
- Bronchiectasis (obstructive or mixed)
- Cystic fibrosis (obstructive or mixed)

**Red Flags**
Severe tachypnea/tachycardia, respiratory muscle fatigue, diminished expiratory effort, cyanosis, silent chest, decreased LOC

Central cyanosis is not detectable until $SaO_2$ is <85%. It is more easily detected in polycythemia and less readily detectable in anemia

## Pathophysiology
- airway obstruction → V/Q mismatch → hypoxemia → ↑ ventilation → ↓ $P_aCO_2$ → ↑ pH and muscle fatigue → ↓ ventilation, ↑ $P_aCO_2$/↓ pH

## Signs and Symptoms
- dyspnea, wheezing, chest tightness, cough, sputum
- symptoms usually occur or worsen at night
- symptoms can be paroxysmal or persistent
- signs of respiratory distress
- pulsus paradoxus

**Table 11. Criteria for Determining if Asthma is Well Controlled**

| | |
|---|---|
| Daytime symptoms <4 d/wk | No asthma-related absence from work/school |
| Night-time symptoms <1 night/wk | β2-agonist use <4 times/wk |
| Physical activity unimpaired by symptoms | $FEV_1$ or PEF >90% of personal best |
| Exacerbations mild, infrequent | PEF diurnal variation <10-15% |

Adapted from: Can Respir J 2012; 19:127-164

**Table 12. Pulmonary Function Criteria for Diagnosis of Asthma**

| Preferred Measurement | Alternative Measurements |
|---|---|
| **Spirometry Showing Reversible Airway Obstruction** | **Peak Expiratory Flow Variability** |
| (1) ↓ $FEV_1$/FVC below lower limit of normal | (1) ↓ in PEF after a bronchodilator or course of controller therapy |
| Adults: <0.75 to 0.8 in adults | Adults: PEF ↑ 60 L/min (min. 20%) OR |
| Children age 6+: <0.8-0.9 | Diurnal variation >8% for twice daily readings (20% for multiple daily readings) |
| AND | Children age 6+: PEF ↑ 20% |
| | **Positive Challenge Test** |
| (2) ↑ $FEV_1$ ≥12% and, 200 mL in adults after bronchodilator or controller therapy | (1) Methacholine challenge: positive if $FEV_1$ ↓ >20% when 4 mg/mL of inhaled methacholine is given; borderline if 4-16 mg/mL is required OR |
| | (2) Post-exercise: ↓ $FEV_1$ ≥10-15% |

Adapted from: Can Respir J 2012; 19:127-164

## Treatment
- environment: avoid triggers
- patient education: features of the disease, goals of treatment, self-monitoring
- pharmacological
  - symptomatic relief in acute episodes: short-acting β2-agonist, anticholinergic bronchodilators, inhaled corticosteroids, addition of a long acting β2-agonist
  - long-term maintenance: inhaled/oral corticosteroids, anti-allergic agents, long-acting β2-agonists (do not use LABA alone), long-acting anticholinergics, methylxanthine, LTRA, anti-IgE antibodies (e.g. omalizumab), anti-IL5 drugs (e.g. mepolizumab) (see Figure 9)

## Emergency Management of Asthma
- see Emergency Medicine, ER29

1. inhaled β2-agonist first line (MDI route and spacer device recommended)
2. systemic steroids (PO or IV if severe)
3. if severe add anticholinergic therapy ± magnesium sulfate
4. rapid sequence intubation in life-threatening cases (plus 100% $O_2$, monitors, IV access)
5. SC/IV adrenaline if caused by anaphylaxis, IV salbutamol if unresponsive
6. corticosteroid therapy at discharge

**Asthma Triggers**
- URTIs
- Allergens (pet dander, house dust, moulds, cockroach)
- Irritants (cigarette smoke, air pollution)
- Drugs (NSAIDs, β-blockers)
- Preservatives (sulphites, MSG)
- Other (emotion/anxiety, cold air, exercise, GERD)

**Signs of Poor Asthma Control**

**"DANGERS"**
**D**aytime Sx ≥4 times/wk
**A**ctivities reduced
**N**ightime Sx ≥1 time/wk
**G**P visits
**E**R visits
**R**escue puffer (SABA) use ≥4 times/wk
**S**chool and work absences

**Asthma Action Plan**
Is a written plan developed by patients and their physicians which includes signs and symptoms for patients to recognize their current level of respiratory distress (denoted as 'green', 'yellow', or 'red/emergency' zones) and the personalized treatment options for each zone

**LTRA in Addition to Usual Care for Acute Asthma in Adults and Children**
Cochrane DB Syst Rev 2012;CD006100
**Purpose**: To determine if the addition of LTRA is beneficial to patients with acute asthma receiving inhaled bronchodilators and systemic corticosteroids.
**Methods**: RCTs in Cochrane Airway Group's Specialised Register of trials that compared LTRA and standard vs. placebo and standard in people with acute asthma of any age.
**Results**: 8 trials, 1470 adults and 470 children. For oral treatment, no significant difference between LTRAs and control in hospital admission (RR 0.86; 95% CI 0.21-3.52) or requirement for additional care (RR 0.87; 95% CI 0.60-1.68). LTRAs improved $FEV_1$ in adults (mean difference 0.08; 95% CI 0.01-0.14) but not in children. No significant difference in adverse events between LTRAs and control (RR 0.81; 95% CI 0.22-2.99). Similar results were found for intravenous treatment.
**Conclusions**: Currently, there is no evidence to support routine use of LTRAs in acute asthma.

## Guidelines for Asthma Management

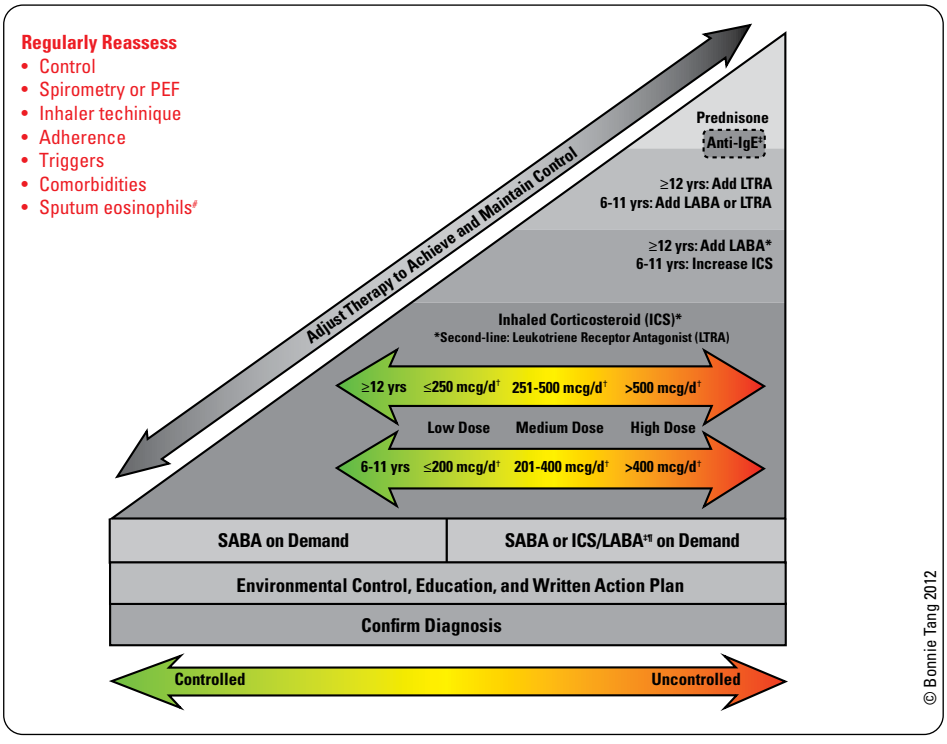



**Figure 9. Guidelines for asthma management**
Adapted from: Can Respir J 2012;19:127-164

# Chronic Obstructive Pulmonary Disease

• see Family Medicine, FM16

## Definition

- progressive and irreversible condition of the lung characterized by chronic obstruction to airflow with many patients having periodic exacerbations, gas trapping, lung hyperinflation, and weight loss
- spirometry required for diagnosis (post-bronchodilator $FEV_1/FVC < 0.70$)
- 2 subtypes: chronic bronchitis and emphysema (usually coexist to variable degrees)
- gradual decrease in $FEV_1$ over time with episodes of acute exacerbations

### Table 13. Clinical and Pathologic Features of COPD*

| Chronic Bronchitis | Emphysema |
|---|---|
| **Defined Clinically**<br>Productive cough on most days for at least 3 consecutive months in 2 successive years<br>Obstruction is due to narrowing of the airway lumen by mucosal thickening and excess mucus<br>Airway changes include increased goblet cells, fibrosis of bronchioles, loss of tethering due to destruction of alveolar walls | **Defined Pathologically**<br>Dilation and destruction of air spaces distal to the terminal bronchiole without obvious fibrosis<br>Decreased elastic recoil of lung parenchyma causes decreased expiratory driving pressure, airway collapse, and air trapping |
| | **2 Types**<br>1) Centriacinar (respiratory bronchioles predominantly affected)<br>Typical form seen in smokers, primarily affects upper lung zones<br>2) **Panacinar** (all parts of acinus)<br>Accounts for about 1% of emphysema cases<br>α1-antitrypsin deficiency, primarily affects lower lobes |

*Note that both chronic bronchitis and emphysema can exist without obstruction. Only if obstruction is also present is it termed COPD.

## Risk Factors

- smoking is the #1 risk factor
- environmental: air pollution, occupational exposure, exposure to wood smoke or other biomass fuel for cooking
- treatable factors: α1-antitrypsin deficiency, bronchial hyperactivity (asthma, chronic bronchitis)
- demographic factors: age, FHx of atopy, history of childhood respiratory infections, low socioeconomic status

Consider LABA for night-time symptoms

**Long-Acting Muscarinic Antagonist Added to LABA/ICS vs. LABA/ICS for Adults with Asthma**
Cochrane DB Syst Rev 2016;CD011721
**Objective**: To assess the effects of adding long-acting muscarinic antagonist to LABA/ICS therapy in adults whose asthma is not well controlled by LABA/ICS.
**Methods**: RCTs in Cochrane Airways Review Group Specialized Register that compared long-acting muscarinic antagonist as an add-on to LABA/ICS vs. LABA/ICS alone for adults with asthma.
**Results**: 4 trials, 1197 adults taking LABA/ICS combination therapy. Individuals taking tiotropium add-on plus LABA/ICS had fewer exacerbations requiring oral steroids than LABA/ICS alone (OR 0.76, 95% CI 0.57-1.02). No difference in quality of life between groups (MD 0.09, 95% CI 0.03-0.2). Inconsistent evidence whether tiotropium increased or decreased serious adverse events in this population (OR 0.60, 95% CI 0.24-1.47). Tiotropium add-on therapy improved lung function, as measured by trough $FEV_1$ (MD 0.07, 95% CI 0.030-0.11) and FVC (MD 0.07, 95% CI 0.020-0.13).
**Conclusions**: Tiotropium may reduce need for rescue oral steroids over LABA/ICS alone in people with severe asthma.

**Natural Progression of COPD**

| | |
|---|---|
| **40s** | Chronic productive cough, wheezing occasionally |
| **50s** | 1st acute chest illness |
| **60s** | Dyspnea on exertion, increasing sputum, more frequent exacerbations |
| **Late Stage** | Hypoxemia with cyanosis, polycythemia, hypercapnia (morning headache), cor pulmonale, weight loss |

**Complications of COPD**
- Polycythemia 2° to hypoxemia
- Chronic hypoxemia
- Pulmonary HTN from vasoconstriction
- Cor pulmonale
- Pneumothorax due to rupture of emphysematous bullae
- Depression
- Bacterial infections

**$CO_2$ Retainers**
On ABG, retainers have chronically elevated $CO_2$ levels with a normal pH. Maintain $O_2$ Sat between 88-92% to prevent Haldane effect, worsening V/Q mismatch, and decreased respiratory drive

Remember, first line therapy for COPD is smoking cessation

**α-1-Antitrypsin Deficiency**
Inherited disorder of defective production of α1-antitrypsin, a protein produced by hepatocytes. Acts in the alveolar tissue by inhibiting the action of proteases from destroying alveolar tissue. When deficient, proteases can destroy lung alveoli resulting in emphysema

## Signs and Symptoms

### Table 14. Clinical Feature and Investigations for Chronic Emphysema

| | Symptoms | Signs | Investigations |
|---|---|---|---|
| **Bronchitis (Blue Bloater*)** | Chronic productive cough<br>Purulent sputum<br>Hemoptysis | Cyanosis (2º to hypoxemia and hypercapnia)<br>Peripheral edema from RVF (cor pulmonale)<br>Crackles, wheezes<br>Prolonged expiration if obstructive<br>Frequently obese | **PFT:**<br>↓ $FEV_1$, ↓ $FEV_1$/FVC<br>N TLC, ↓ or N $DL_{CO}$<br>**CXR:**<br>AP diameter normal<br>↑ bronchovascular markings<br>Enlarged heart with cor pulmonale |
| **Emphysema (Pink Puffer*)** | Dyspnea (± exertion)<br>Minimal cough<br>Tachypnea<br>Decreased exercise tolerance | Pink skin<br>Pursed-lip breathing<br>Accessory muscle use<br>Cachectic appearance due to anorexia and increased work of breathing<br>Hyperinflation/barrel chest<br>Hyperresonant percussion<br>Decreased breath sounds<br>Decreased diaphragmatic excursion | **PFT:**<br>↓ $FEV_1$, ↓ $FEV_1$/FVC<br>↑ TLC (hyperinflation)<br>↑ RV (gas trapping)<br>↓ $DL_{CO}$<br>**CXR:**<br>↑ AP diameter<br>Flat hemidiaphragm (on lateral CXR)<br>↓ cardiac silhouette<br>↑ retrosternal space<br>Bullae<br>↓ peripheral vascular markings |

*Note that the distinction between "blue bloaters" and "pink puffers" is more of historical than practical interest as most COPD patients have elements of both

### Table 15. Treatment of Stable COPD

| Treatment | Details |
|---|---|
| **PROLONG SURVIVAL** | |
| **Smoking Cessation** | Nicotine replacement, bupropion, varenicline |
| **Vaccination** | Annual influenza vaccination, pneumococcal vaccination |
| **Home Oxygen** | Prevents cor pulmonale and decreases mortality if used >15h/d; indicated if:<br>(1) $PaO_2$ <55 mmHg or<br>(2) $PaO_2$ <60 mmHg with cor pulmonale or polycythemia |
| **SYMPTOMATIC RELIEF (no mortality benefit)** | |
| **Bronchodilators** (mainstay of current drug therapy, used in combination) | Short-acting anticholinergics (e.g. ipratropium bromide) and short-acting β2-agonists (e.g. salbutamol, terbutaline) |
| | SABAs: rapid onset but significant side effects at high doses (e.g. hypokalemia) |
| | Short-acting anticholinergics slightly more effective than SABAs with fewer side effects but slower onset |
| | Using a combination of both is superior to monotherapy |
| | LABAs (e.g. salmeterol, formoterol, indacaterol) and long-acting anticholinergics (e.g. tiotropium bromide, glycopyrronium bromide) |
| | More sustained effects for moderate to severe COPD |
| | LAMAs more effective at decreasing exacerbation rates than LABAs |
| | Using a combination of both is superior than monotherapy |
| | Inhaled corticosteroid (ICS) + LABA combination (e.g. Advair®: fluticasone + salmeterol, Symbicort®: budesonide + formoterol) |
| | Theophylline: weak bronchodilator; limited evidence to suggest combination with bronchodilator |
| | Side effects: nervous tremor, nausea/vomiting/diarrhea, tachycardia, arrhythmias, sleep changes |
| | PDE4 inhibitor: roflumilast (Daxas®) anti-inflammatory medication useful in COPD with chronic bronchitis, severe airflow obstruction, frequent exacerbations |
| **Corticosteroids** | ICS monotherapy has been shown to increase the incidence of pneumonia in COPD; ICS should only be used with a LABA in combination in patients with a history of exacerbations |
| | Oral steroids are important when treating exacerbations; chronic systemic glucocorticoids are generally not recommended due to unfavourable benefit to risk ratio |
| **Surgical** | Lung volume reduction surgery (resection of emphysematous parts of lung, associated with higher mortality if $FEV_1$ <20%), lung transplant |
| **Other** | Patient education, eliminate respiratory irritants/allergens (occupational/environmental), exercise rehabilitation to improve physical endurance |

**GOLD Classification of the Severity of COPD**
GOLD 1 Mild $FEV_1$ ≥80% of predicted
GOLD 2 Moderate 50% ≤$FEV_1$ <80% of predicted
GOLD 3 Severe 30% ≤ $FEV_1$ <50% of predicted
GOLD 4 Very Severe $FEV_1$ <30% of predicted
Note: Use COPD Assessment Tool for comprehensive assessment of symptoms, weak correlation between FEV1 and symptoms

Remember to step down therapy to lowest doses which control symptoms/signs of bronchoconstriction

**Influenza Vaccine for Patients with Chronic Obstructive Pulmonary Disease**
Cochrane DB Syst Rev 2006;1:CD002733
**Study**: Cochrane Systematic Review. 11 RCTs included, 6 specifically in COPD patients.
**Population**: Six of the studies were done on COPD patients in particular, while the others were on elderly and high-risk individuals. Asthma patients were excluded.
**Intervention**: Live or inactivated virus vaccines vs. placebo.
**Outcome**: Exacerbation rates, hospitalizations, mortality, lung function and adverse effects.
**Results**: In patients with COPD, inactive vaccine correlated with fewer exacerbations per vaccinated subject than placebo (weighted mean difference (WMD) -0.37, 95% CI -0.64 to -0.11). Inactivated vaccine resulted in fewer influenza-related infections than placebo (WMD 0.19, 95% CI 0.07-0.48). There was also an increased risk of local mild, transient adverse reactions with the vaccine.
**Conclusions**: There appears to be a reduction in influenza-related infections, as well as exacerbations in patients with COPD receiving the vaccine.

**Systemic Corticosteroids for Acute Exacerbations of Chronic Obstructive Pulmonary Disease**
Cochrane DB Syst Rev 2014;9:CD001228
**Study**: Cochrane systematic review 16 studies.
**Population**: 1787 patients with acute COPD exacerbations.
**Intervention**: Oral or parenteral corticosteroids vs. placebo.
**Outcome**: Treatment failure, risk of relapse, time to next COPD exacerbation, likelihood of adverse event, length of hospital stay, and lung function at end of treatment.
**Results**: Systemic corticosteroids reduced the risk of treatment failure by over half compared with placebo in nine studies (n = 917) with median treatment duration 14 d, odds ratio (OR) 0.48 (95% CI 0.35-0.67). The evidence was graded as high quality and it would have been necessary to treat nine people (95% CI 7-14) with systemic corticosteroids to avoid one treatment failure. There was moderate-quality evidence for a lower rate of relapse by 1 mo for treatment with systemic corticosteroid in two studies (n = 415) (hazard ratio (HR) 0.78; 95% CI 0.63-0.97). Mortality up to 30 d was not reduced by treatment with systemic corticosteroid compared with control in 12 studies (n = 1319; OR 1.00; 95% CI 0.60-1.66). FEV1, measured up to 72 hours, showed significant treatment benefits (7 studies; n = 649; mean difference (MD) 140 mL; 95% CI 90-200); however, this benefit was not observed at later time points. The likelihood of adverse events increased with corticosteroid treatment (OR 2.33; 95% CI 1.59-3.43). The risk of hyperglycemia was significantly increased (OR 2.79; 95% CI 1.86-4.19). For general inpatient treatment, duration of hospitalization was significantly shorter with corticosteroid treatment (MD -1.22 d; 95% CI -2.26 to -0.18), with no difference in length of stay in the intensive care unit (ICU) setting. Comparison of parenteral versus oral treatment showed no significant difference in the primary outcomes of treatment failure, relapse or mortality or for any secondary outcomes.
**Conclusion**: There is high-quality evidence to support treatment of exacerbations of COPD with systemic corticosteroid by the oral or parenteral route in reducing the likelihood of treatment failure and relapse by 1 mo, shortening length of stay in hospital inpatients not requiring assisted ventilation in ICU and giving earlier improvement in lung function and symptoms. There is no evidence of benefit for parenteral treatment compared with oral treatment with corticosteroid on treatment failure, relapse or mortality. There is an increase in adverse drug effects with corticosteroid treatment, which is greater with parenteral administration compared with oral treatment.

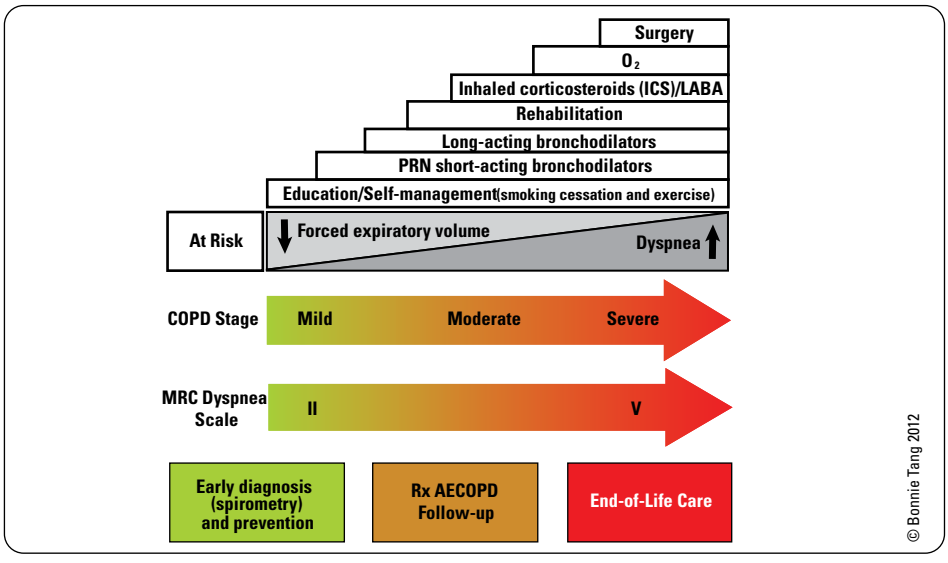



**Figure 10. Guidelines for COPD management**
Adapted from: Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease. Can Respir J 2008;(Suppl A):15

## Acute Exacerbations of COPD

- **definition**
  - sustained (>48 h) worsening of dyspnea, cough, or sputum production leading to an increased use of medications
  - in addition, defined as either purulent or non-purulent (to predict need for antibiotic therapy)
- **etiology**: viral URTI, bacteria, air pollution, CHF, PE, MI must be considered
- **management**
  - ABCs, consider assisted ventilation if decreasing LOC or poor ABGs
  - $O_2$: target 88-92% $SaO_2$ for $CO_2$ retainers
  - bronchodilators by MDI with spacer or nebulizer
    - SABA + anticholinergic, e.g. salbutamol and ipratropium bromide via nebulizers × 3 back-to-back q15min
  - systemic corticosteroids: IV solumedrol or oral prednisone
  - antibiotics for exacerbations with sputum purulence, ICU admission, or non-invasive ventilation (NIV use)
    - 1st line: Amoxicillin-Clavulanic Acid
    - if allergic to penicillin, fluoroquinolone or doxycycline
  - post exacerbation: rehabilitation with general conditioning to improve exercise tolerance
- ICU admission
  - for life-threatening exacerbations
  - ventilatory support
    - non-invasive: NIPPV, BiPAP
    - conventional mechanical ventilation

## Prognosis in COPD

- prognostic factors
  - level of dyspnea is the single best predictor
  - development of complications, e.g. hypoxemia or cor pulmonale
- 5 yr survival
  - $FEV_1$ <1 L = 50%
  - $FEV_1$ <0.75 L = 33%
- **BODE** index for risk of death in COPD
  - greater score = higher probability the patient will die from COPD; score can also be used to predict hospitalization
  - 10 point index consisting of four factors:
    - **B**ody mass index (BMI): ≤21 (+1 point)
    - **O**bstruction ($FEV_1$): 50-64% (+1), 36-49% (+2), <35% (+3)
    - **D**yspnea (MRC scale): walks slower than people of same age on level surface, stops occasionally (+1), stops at 100 yards or a few minutes on the level (+2), too breathless to leave house or breathless when dressing/undressing (+3)
    - **E**xercise capacity (6 minute walk distance): 250-349 m (+1), 150-249 m (+2), <149 m (+3)

**Pulmonary Embolism in Patients with Unexplained Exacerbation of COPD: Prevalence and Risk Factors**
Ann Intern Med 2006;144:390-96
**Study**: Prospective cohort study of 211 patients with COPD (all current and former smokers) admitted to hospital for severe COPD exacerbation of unknown origin.
**Measurements**: All patients received spiral CT angiogram (CTA) and venous compression ultrasonography of both legs.
**Results**: 25% of patients met diagnostic criteria for PE (+ CTA or + U/S).
**Conclusions**: Prevalence of PE in patients hospitalized for COPD exacerbation of unknown origin is 25%. Therefore, all patients presenting to hospital with COPD exacerbation without obvious cause require PE workup (leg dopplers or CTA – decision of which to use depends on pre-test probability of the patient).

**Non-Invasive Ventilation for the Management of Acute Hypercapnic Respiratory Failure due to Exacerbation of COPD**
Cochrane DB Syst Rev 2017; 7:CD004104
**Objective**: To compare efficacy of non-invasive ventilation (NIV) in conjunction with usual care vs. usual care alone in adults with acute hypercapnic respiratory failure secondary to acute exacerbation of COPD.
**Methods**: RCTs in Cochrane Airways Group Specialized Register that compared usual care plus non-invasive ventilation vs. usual care alone in acute hospital setting for adult patients with mean admission pH <7.35 and $PaCO_2$ >45 mmHg.
**Results**: 17 trials, 1264 adult patients. Addition of NIV decreased risk of mortality (RR 0.54, 95% CI 0.38-0.76) and risk of needing endotracheal intubation (RR 0.36, 95% CI 0.28-0.46). NIV plus usual care was also associated with reduced length of hospital stay (MD -3.39d, 95% CI -5.93 - -0.85), reduced incidence of complications (RR 0.26, 95% CI 0.13-0.53), improvement of pH (MD 0.05, 95% CI 0.02-0.07), and improvement of $PaO_2$ (MD 7.47 mmHg, 95% CI -11.05-1.80 mmHg).
**Conclusions**: NIV in conjunction with usual care is beneficial as first-line intervention in patients admitted with acute hypercapnic respiratory failure secondary to acute exacerbation of COPD.

**Different Durations of Corticosteroid Therapy for Exacerbations of Chronic Obstructive Pulmonary Disease**
Cochrane DB Syst Rev 2014;12:CD006897
**Study**: Cochrane systematic review. 8 studies.
**Population**: 582 patients, with severe or very severe COPD.
**Intervention**: Corticosteroids given at equivalent daily doses for 3-7 d (short duration) vs. 10-15 d (longer-duration).
**Outcome**: Treatment failure, risk of relapse, time to next COPD exacerbation, likelihood of adverse event, length of hospital stay, and lung function at end of treatment.
**Results**: In four studies there was no difference in risk of treatment failure between short-duration and longer-duration systemic corticosteroid treatment (n = 457; odds ratio (OR) 0.72, 95% confidence interval (CI) 0.36-1.46)), which was equivalent to 22 fewer per 1000 for short-duration treatment (95% CI 51 fewer to 34 more). No difference in risk of relapse (a new event) was observed between short-duration and longer-duration systemic corticosteroid treatment (n = 457; OR 1.04, 95% CI 0.70-1.56), which was equivalent to nine fewer per 1000 for short-duration treatment (95% CI 68 fewer to 100 more). Time to the next COPD exacerbation did not differ in one large study that was powered to detect non-inferiority and compared 5 d versus 14 d of systemic corticosteroid treatment (n = 311; hazard ratio 0.95, 95% CI 0.66 to 1.37). In five studies no difference in the likelihood of an adverse event was found between short-duration and longer-duration systemic corticosteroid treatment (n = 503; OR 0.89, 95% CI 0.46-1.69, or nine fewer per 1000 [95% CI 44 fewer to 51 more]). Length of hospital stay (n = 421; mean difference (MD) -0.61 d, 95% CI -1.51-0.28) and lung function at the end of treatment (n = 185; MD $FEV_1$ -0.04 L; 95% CI -0.19-0.10) did not differ between short-duration and longer-duration treatment.
**Conclusion**: 5 d of oral corticosteroids is likely to be sufficient for treatment of adults with acute exacerbations of COPD, and this review suggests that the likelihood is low that shorter courses of systemic corticosteroids (of around five days) lead to worse outcomes than are seen with longer (10 to 14 d) courses.

# Bronchiectasis

## Definition
- irreversible dilatation of airways due to inflammatory destruction of airway walls resulting from persistently impaired mucous clearance and infected mucus
- usually affects medium sized airways
- the most common sputum pathogens in non-cystic fibrosis patients are *H. influenzae, P. aeruginosa*, and *M. catarrhalis*

**Table 16. Etiology and Pathophysiology of Bronchiectasis**

| Obstruction | Post-Infectious (results in dilatation of bronchial walls) | Impaired Defenses (leads to interference of drainage, chronic infections, and inflammation) |
|---|---|---|
| Tumour | Pneumonia | Hypogammaglobulinemia |
| Foreign body | TB | CF |
| | Measles | Defective leukocyte function |
| | Pertussis | Ciliary dysfunction |
| | Allergic bronchopulmonary aspergillosis | (Kartagener's syndrome: bronchiectasis, sinusitis, situs inversus) |
| | Nontuberculous mycobacterium (NTM) | |

## Signs and Symptoms
- chronic cough, copious purulent sputum (but 10-20% have dry cough), dyspnea, fatigue, chronic rhinosinusitis, hemoptysis (can be massive), recurrent pneumonia, local crackles (inspiratory and expiratory), rhonchi, wheezes
- may be difficult to differentiate from chronic bronchitis

## Investigations
- PFTs: often demonstrate obstructive pattern but may be normal
- CXR
  - nonspecific: increased markings, linear atelectasis, loss of volume in affected areas
  - specific: "tram tracking" – parallel narrow lines radiating from hilum, cystic spaces, honeycomb like structures
- high-resolution thoracic CT (diagnostic, gold standard)
  - 87-97% sensitivity, 93-100% specificity
  - "signet ring": dilated bronchi with thickened walls where diameter bronchus >1.5x diameter of accompanying artery
- sputum cultures (routine + AFB)
- CBC
- LFTs
- immunoglobin panel (serum Ig levels)
- sweat chloride if cystic fibrosis suspected (upper zone predominant)

## Treatment
- vaccination: influenza and pneumococcal vaccination
- chest physiotherapy, breathing exercises, physical exercise
- antibiotics (oral, IV, inhaled):
  - inhaled: used chronically to decrease bacterial load, driven by sputum bacteriology
  - oral/IV: routinely used for exacerbations, driven by sputum sensitivity; macrolides may be used chronically for an anti-inflammatory effect chronically
- mucolytics (e.g. hypertonic saline)
- inhaled corticosteroids: decrease inflammation, however, may increase risk of exacerbations
- oral corticosteroids for acute, major exacerbations
- pulmonary resection: in selected cases with focal bronchiectasis
- transplant: for end stage diffuse causes (e.g. PCD etc.)

# Cystic Fibrosis

- see Pediatrics, P82

## Pathophysiology
- chloride transport dysfunction: thick secretions from exocrine glands (lung, pancreas, skin, reproductive organs) and blockage of secretory ducts

## Clinical Features
- multisystem: results in severe lung disease, pancreatic insufficiency, salt loss syndrome, and azoospermia
- other manifestations: meconium ileus in infancy, distal ileal obstruction in adults, CF related diabetes, sinusitis, liver disease, bone disease, malnutrition
- chronic lung infections
  - *S. aureus* and *H. influenzae*: early
  - *P. aeruginosa*: most common in adulthood
  - *B. cepacia* complex: worse prognosis (some subtypes) so infection control is key
  - In adults, colonization with more resistant bacteria increases (eg. PsA, Burkholderia cepacia complex, Stenotrophomonas, Achromobacter, MRSA, NTM etc.)



Usually presents in childhood as recurrent lung infections that become persistent and chronic

### Investigations
- Genetic testing
  - autosomal recessive- more than 2100 mutations in CFTR described, not all disease causing
- Sweat chloride test
  - increased concentrations of NaCl and $K^+$ ($[Cl^-]$ >60 mmol/L on two occasions supports the diagnosis)
  - carriers have normal sweat tests (and no symptoms)
- PFTs
  - early: airflow limitation in small airways
  - late: severe airflow obstruction, hyperinflation, gas trapping, decreased $DL_{CO}$ (very late)
- ABGs
  - hypoxemia, hypercapnia later in disease with eventual respiratory failure and cor pulmonale
- CXR
  - hyperinflation, increased pulmonary markings (especially upper lobes)

### Treatment
- chest physiotherapy
- pancreatic enzyme replacements, high fat, high calorie diet
- bronchodilators (salbutamol ± ipratropium bromide)
- inhaled mucolytic (reduces mucus viscosity), hypertonic saline, DNase
- inhaled antibiotics (tobramycin, colistin, aztreonam, levofloxacin, vancomycin)
- anti-inflammatory medications (e.g. azithromycin, ICS in some)
- antibiotics oral and IV (targeted to sputum growth e.g. ciprofloxacin for *Pseudomonas*)
- CFTR potentiators and modulators (e.g. Ivacaftor, Orkambi, Symdeko)
- lung transplant

### Prognosis
- depends on: infections (*B. cepacia* colonization), $FEV_1$, acute pulmonary exacerbations, lung transplant vs. non-lung transplant
- female gender and low socioeconomic class have greater risk of early death

# Interstitial Lung Disease

### Definition
- a group of disorders which cause progressive scarring of lung tissue and impair lung function and gas exchange

### Pathophysiology
- inflammatory and/or fibrosing process in the alveolar walls → distortion and destruction of normal alveoli and microvasculature
- typically associated with:
  - lung restriction (decrease in TLC and VC)
  - decreased lung compliance (increased or normal $FEV_1/FVC$)
  - impaired diffusion (decreased $DL_{CO}$)
  - hypoxemia due to V/Q mismatch (usually without hypercapnia until end stage)
  - pulmonary HTN and cor pulmonale occur with advanced disease secondary to hypoxemia and blood vessel destruction

### Etiology
- >100 known disorders can cause ILD
- majority due to unknown agents or cause



**In ILD think**
**FASSTEN** and **BAD RASH**

**Upper Lung Disease (FASSTEN)**
**F**armer's lung (hypersensitivity pneumonitis)
**A**nkylosing spondylitis
**S**arcoidosis
**S**ilicosis
**TB**
**E**osinophilic granuloma (Langerhans-cell histiocytosis)
**N**eurofibromatosis

**Lower Lung Disease (BADRASH)**
**B**ronchiolitis obliterans with organizing pneumonia (BOOP)/Cryptogenic Organizing Pneumonia (COP)
**A**sbestosis
**D**rugs (nitrofurantoin, hydralazine, INH, amiodarone, many chemo drugs)
**R**heumatologic disease
**A**spiration
**S**cleroderma
**H**amman Rich (acute interstitial pneumonia) and IPF

**Table 17. Interstitial Lung Diseases**

| UNKNOWN ETIOLOGY | KNOWN ETIOLOGY | | |
|---|---|---|---|
| Idiopathic interstitial pneumonias | **ILD Associated with Systemic Rheumatic Disorders** | **ILD Associated with Drugs or Treatments** | **Inherited Disorders** |
| UIP (usual interstitial pneumonia e.g. IPF) | Scleroderma | Antibiotics (nitrofurantoin) | Familial IPF |
| NSIP (non-specific interstitial pneumonia) | Rheumatoid arthritis | Anti-inflammatory agents (methotrexate) | Telomerase mutations |
| LIP (lymphocytic interstitial pneumonia) | SLE | Cardiovascular drugs (amiodarone) | Neurofibromatosis |
| COP (cryptogenic organizing pneumonia e.g. BOOP) | Polymyositis/dermatomyositis | Antineoplastic agents (chemotherapy agents) | Tuberous sclerosis |
| DIP (desquamative interstitial pneumonia) | Anti-synthetase syndromes | Illicit drugs (e.g. crack lung, talc granulomatosis) | Gaucher's disease |
| IPPFE (idiopathic pleuroparenchymal fibroelastosis) | Mixed connective tissue disease | Radiation | **Alveolar Filling Disorders** |
| AFOP (acute fibrinous and organizing pneumonia) | **Environment/Occupation Associated ILD** | **ILD Associated with Pulmonary Vasculitis** | Chronic eosinophilic pneumonia |
| Sarcoidosis | Hypersensitivity pneumonitis (usually organic antigen) | Granulomatosis with Polyangiitis (GPA) | Pulmonary alveolar proteinosis |
| Langerhans-cell histiocytosis (eosinophilic granuloma) | Farmer's lung | Goodpasture's syndrome | |
| Lymphangioleiomyomatosis | Air conditioner/humidifier lung | Idiopathic pulmonary hemosiderosis | |
| | Bird breeder's lung | | |
| | Pneumoconioses (inorganic dust) | | |
| | Silicosis | | |
| | Asbestosis | | |
| | Coal worker's pneumoconiosis | | |
| | Chronic beryllium disease | | |
| | Pneumonitis from gases/fumes/vapour | | |

## Signs and Symptoms

- dyspnea, especially on exertion
- nonproductive cough
- crackles (dry, fine, end-inspiratory)
- clubbing (especially in IPF and asbestosis)
- features of cor pulmonale
- note that signs and symptoms vary with underlying disease process
  - e.g. sarcoidosis is seldom associated with crackles and clubbing

## Investigations

- CXR/high resolution CT (see Medical Imaging, MI6)
  - usually decreased lung volumes
  - reticular, nodular, or reticulonodular pattern (nodular <3 mm)
  - hilar/mediastinal adenopathy (bilateral especially in sarcoidosis)
  - honeycombing (pathognomonic for UIP)
- PFTs
  - restrictive pattern: decreased lung volumes and compliance
  - normal or increased $FEV_1/FVC$ (>70-80%), e.g. flow rates are often normal or high when corrected for absolute lung volume
  - $DL_{CO}$ decreased due to V/Q mismatch (less surface area for gas exchange ± pulmonary vascular disease) and diffusion impairment
- ABGs
  - hypoxemia and respiratory alkalosis may be present with progression of disease
- other
  - bronchoscopy, bronchoalveolar lavage, lung biopsy
  - RF (RA), anti-CCP, connective tissue disease (CTD) screen, serum-precipitating antibodies to inhaled organic antigens (hypersensitivity pneumonitis), c-ANCA (GPA), anti-GBM (Goodpasture's)



The CXR can be normal in up to 15% of patients with interstitial lung disease

# Unknown Etiologic Agents

## IDIOPATHIC PULMONARY FIBROSIS

### Definition
- pulmonary fibrosis of unknown cause with usual interstitial pneumonia (UIP) histology (found on biopsy or inferred from CT)
- a progressive, irreversible condition
- DDx: NSIP, COP, desquamative interstitial pneumonitis (DIP), lymphocytic interstitial pneumonitis (LIP), Sjögren's disease

### Signs and Symptoms
- commonly presents over age 50, incidence rises with age; males > females
- dyspnea on exertion, nonproductive cough, constitutional symptoms, late inspiratory fine crackles at lung bases, clubbing

### Investigations
- labs (nonspecific, autoimmune serology usually negative)
- CXR: reticular or reticulonodular pattern with lower lung predominance; often see honeycombing in advanced disease
- high resolution CT: lower zone peripheral reticular markings, traction bronchiectasis, honeycombing; ground glass, consolidation, or nodules should not be prominent in IPF
- biopsy: rarely for UIP as honeycombing usually makes diagnosis possible based on radiologic findings alone

### Treatment
- $O_2$
- pirfenidone and nintedanib can slow disease progression
- lung transplantation for advanced disease
- mean survival of 3-5 yr after diagnosis

**IPF Prevalence**
- Age 35-44: 2-7 per 100,000
- Age >75: 175 per 100,000

**Effect of Pirfenidone on Mortality: Pooled Analyses and Meta-analyses of Clinical Trials in Idiopathic Pulmonary Fibrosis**
Lancet Respir Med 2017;5:33-41
**Objectives**: To compare mortality outcomes over 120 weeks in patients with idiopathic pulmonary fibrosis on pirfenidone vs. placebo.
**Methods**: Pooled analysis of 3 global randomized phase III trials (CAPACITY 004 and 006, ASCEND 016, and SP2 and SP3).
**Results**: All-cause mortality (HR 0.52, 95% CI 0.31-0.87), treatment-emergent all-cause mortality (HR 0.45, 95% CI 0.24-0.83), idiopathic pulmonary fibrosis related mortality (HR 0.35, 95% CI 0.17-0.72), and treatment-emergent idiopathic pulmonary fibrosis (HR 0.32, 95% CI 0.14-0.76) related mortality was reduced in the pirfenidone group vs. placebo.
**Conclusions**: Pirfenidone therapy is associated with reduction in the relative risk of mortality compared to placebo over 120 wk.

## SARCOIDOSIS

### Definition
- idiopathic non-infectious granulomatous multi-system disease with lung involvement in 90%
- characterized pathologically by non-necrotizing granulomas (although occasionally necrosis is present)
- numerous HLA antigens and other genetic markers have been shown to play a role and familial sarcoidosis is now recognized

### Epidemiology
- typically affects young and middle-aged patients
- higher incidence among people of African descent (in USA) and from northern latitudes e.g. Scandinavia, Canada

### Signs and Symptoms
- asymptomatic, cough, dyspnea, fever, arthralgia, malaise, erythema nodosum, chest pain
- chest exam often normal
- common extrapulmonary manifestations
  - eye involvement (anterior or posterior uveitis)
  - skin involvement (skin papules, erythema nodosum, lupus pernio)
  - peripheral lymphadenopathy
  - arthralgia
  - hepatomegaly ± splenomegaly
  - less common extra-pulmonary manifestations involve bone, CNS, kidney, cardiac (arrhythmias, sudden death, CHF)
- two acute sarcoid syndromes
  - Lofgren's syndrome: fever, erythema nodosum, bilateral hilar lymphadenopathy, arthralgias
  - Heerfordt-Waldenstrom syndrome: fever, parotid enlargement, anterior uveitis, facial nerve palsy

### Investigations
- CBC (cytopenias from spleen or marrow involvement, lymphopenia common)
- serum electrolytes, creatinine, liver enzymes, calcium (hypercalcemia/hypercalciuria due to vitamin D activation by granulomas)
- hypergammaglobulinemia, occasionally RF positive
- elevated serum ACE (non-specific and non-sensitive) – reflects total body granuloma load
- CXR: predominantly nodular opacities especially in upper lung zones ± hilar adenopathy
- PFTs: normal, obstructive pattern, restrictive pattern with normal flow rates and decreased $DL_{CO}$, or mixed obstructive/restrictive pattern
- ECG: to rule out conduction abnormalities
- slit-lamp eye exam: to rule out uveitis

Most common presentation of sarcoidosis: asymptomatic CXR finding

### Diagnosis
- biopsy
  - transbronchial lung biopsy, transbronchial lymph node aspiration, endobronchial ultrasound guided surgical (EBUS) biopsy, or mediastinoscopic lymph node biopsy for granulomas
  - in ~75% of cases, transbronchial biopsy shows granulomas in the parenchyma even if the CXR is normal

### Staging
- radiographic, based on CXR
  - Stage 0: normal radiograph
  - Stage I: bilateral hilar lymphadenopathy ± paratracheal lymphadenopathy
  - Stage II: bilateral hilar lymphadenopathy with pulmonary infiltration
  - Stage III: pulmonary infiltration alone (reticulonodular pattern or nodular pattern)
  - Stage IV: pulmonary fibrosis (loss of volume in upper lobes common, honeycombing uncommon)

### Treatment
- 85% of stage I resolve spontaneously within 2 yr, 50% of stage II resolve spontaneously within 5 yr
- treat with prednisone if severe and/or progressive
- steroids for symptoms, declining lung function, hypercalcemia, or involvement of eye, CNS, kidney, or heart (not for abnormal CXR alone)
- methotrexate or other immunosuppressives can be used as steroid sparing agents in place of long term prednisone

### Prognosis
- approximately 10% mortality secondary to progressive fibrosis of lung parenchyma



Hilar adenopathy refers to enlargement of mediastinal lymph nodes which is most often seen by standard CXR as spherical/ellipsoidal and/or calcified nodes. If unilateral - think neoplasia, TB, or sarcoid. If bilateral - think sarcoid or lymphoma



**Corticosteroids for Pulmonary Sarcoidosis**
Cochrane DB Syst Rev 2005;2:CD001114
**Study**: Meta-analysis of 13 RCTs involving 1066 participants examining the use of steroids (oral or inhaled) in sarcoidosis.
**Results**: Oral steroids demonstrated an improvement in CXR (RR 1.46, 95% CI 1.01-2.09). For inhaled corticosteroids, two studies showed no improvement in lung function and one study showed an improvement in diffusing capacity. No data on side-effects.
**Conclusions**: Oral steroids improve CXR findings and global scores of CXR, symptoms, and spirometry over 3-24 mo, but do not improve lung function or modify disease course. Oral steroids may be of benefit for patients with Stage 2 and 3 disease.

# Known Etiologic Agents

## HYPERSENSITIVITY PNEUMONITIS
- also known as extrinsic allergic alveolitis
- non-IgE mediated inflammation of lung parenchyma (acute, subacute, and chronic forms) - Type 4 hypersensitivity reaction
- caused by sensitization to inhaled agents, usually organic dust
- pathology: airway-centred, poorly formed granulomas, and lymphocytic inflammation
- exposure usually related to occupation or hobby
  - Farmer's Lung (*Thermophilic actinomycetes*)
  - Bird Breeder's/Bird Fancier's Lung (immune response to bird IgA)
  - Humidifier Lung (*Aureobasidium pullulans*)
  - Sauna Taker's Lung (*Aureobasidium* spp.)
  - Popcorn lung (diacetyl)

### Signs and Symptoms
- acute presentation: (4-6 h after exposure)
  - dyspnea, cough, fever, chills, malaise (lasting 18-24 h)
  - CXR: diffuse infiltrates
  - type III (immune complex) reaction
- subacute presentation: more insidious onset than acute presentation
- chronic presentation
  - insidious onset
  - dyspnea, cough, malaise, anorexia, weight loss
  - PFTs: progressively restrictive
  - CXR: predominantly upper lobe reticulonodular pattern
- in both acute and chronic reactions, serum precipitins may be detectable (neither sensitive nor specific)

### Treatment
- early diagnosis: avoidance of further exposure is critical as chronic changes are irreversible
- systemic corticosteroids can relieve symptoms and speed resolution

## PNEUMOCONIOSES
- reaction to inhaled inorganic dusts 0.5-5 μm in size
- no effective treatment, therefore key is exposure prevention through the use of protective equipment
- smoking cessation, annual influenza and pneumococcal vaccination, rehabilitation, lung transplant for endstage disease



Calcified diaphragmatic plaques are highly suggestive of asbestosis, especially if bilateral



**CXR Fibrotic Patterns**
- Asbestosis: lower > upper lobes
- Silicosis: upper > lower lobes
- Coal: upper > lower lobes

**Table 18. Pneumoconioses**

| Diagnosis | Etiology | Signs/Symptoms | Investigations | Complications |
|---|---|---|---|---|
| **Asbestosis** | Exposure risks: insulation, shipyard, construction, brake linings, pipe fitters, plumbers<br>Slowly progressive diffuse interstitial fibrosis induced by inhaled asbestos fibres<br>Usually requires >10-20 yr of exposure<br>Latency period: 20-30 yr | Insidious onset<br>Dyspnea<br>Cough: paroxysmal, non-productive<br>Clubbing (much more likely in asbestosis than silicosis or CWP) | CXR<br>Lower > upper lobe<br>Reticulonodular pattern, may develop IPF-like honeycombing<br>Asbestos exposure can also cause pleural and diaphragmatic plaques (± calcification), pleural effusion, round atelectasis<br>Microscopic examination reveals ferruginous bodies: yellow-brown rod-shaped structures which represent asbestos fibres coated in macrophages | Asbestos exposure increases risk of bronchogenic CA and malignant mesothelioma<br>Risk of lung cancer dramatically increased for smokers |
| **Silicosis** | At risk population: sandblasters, rock miners, stone cutters, quarry and highway workers<br>Generally requires >20 yr exposure; may develop with much shorter but heavier exposure | Dyspnea, cough, and wheezing | CXR<br>Upper > lower lobe<br>Early: nodular disease (simple pneumoconiosis), lung function usually normal<br>Late: nodules coalesce into masses (progressive massive fibrosis)<br>Possible hilar lymph node enlargement (frequently calcified), especially "egg shell" calcification | Mycobacterial infection (e.g. TB) |
| **Coal Worker's Pneumoconiosis (CWP)** | At risk population: coal workers, graphite workers<br>Coal and silica, coal is less fibrogenic than silica | Simple CWP<br>No signs or symptoms, usually normal lung function<br>Complicated CWP (also known as progressive massive fibrosis)<br>Dyspnea<br>Course: few patients progress to complicated CWP | Simple CWP<br>CXR: multiple nodular opacities, mostly upper lobe<br>Pathologic hallmark is coal macule<br>Complicated CWP<br>CXR: opacities larger and coalesce | |



Remember to involve occupational health and place of work for data collection and treatment plan.
Also counsel re: worker's insurance as per jurisdiction (e.g. Workers Safety Insurance Board [WSIB] in Ontario)

## INTERSTITIAL LUNG DISEASE ASSOCIATED WITH DRUGS OR TREATMENTS

### Drug-Induced

- antineoplastic agents: bleomycin, mitomycin, busulfan, cyclophosphamide, methotrexate, chlorambucil, BCNU (carmustine)
- antibiotics: nitrofurantoin, penicillin, sulfonamide
- cardiovascular drugs: amiodarone, tocainide
- anti-inflammatory agents: methotrexate, penicillamine
- gold salts
- illicit drugs (heroin, methadone)
- rituximab, anti-TNF-α agents (infliximab, etanercept, adalimumab)

### Radiation-Induced

- early pneumonitis: approximately 6 wk post-exposure
- late fibrosis: 6-12 mo post-exposure
- infiltrates conform to the shape of the radiation field

# Pulmonary Vascular Disease

## Pulmonary Hypertension

### Definition

- mean pulmonary arterial pressure >25 mmHg at rest and >30 mmHg with exercise, or a systolic pulmonary artery pressure of >40 mmHg at rest
- pulmonary HTN is grouped into 5 categories and classified based on etiology

**Table 19. World Health Organization Classification of Pulmonary Hypertension**

| Classification | Some Causes | Treatment Options | Consider in All Patients with PH |
|---|---|---|---|
| **I. Pulmonary Arterial HTN** | Idiopathic<br>Collagen vascular disease (scleroderma, SLE, RA)<br>Congenital systemic-to-pulmonary shunts (Eisenmenger syndrome)<br>Persistent pulmonary hypertension of the newborn (PPHN)<br>Portopulmonary HTN<br>HIV infection<br>Drugs and toxins (e.g. anorexigens)<br>Pulmonary veno-occlusive disease<br>Schistosomiasis<br>Pulmonary capillary hemangiomatosis | Calcium channel blockers (CCBs) for patients with vasoreactivity. Advanced therapy with prostanoids, endothelin receptor antagonists (ERA), PDE5 inhibitors. Lung transplantation for refractory advanced patients | Oxygen therapy<br>Exercise<br>Consider anticoagulation |
| **II. Pulmonary HTN due to Left Heart Disease** | Left-sided atrial or ventricular heart disease (e.g. LV dysfunction)<br>Left-sided valvular heart disease (e.g. aortic stenosis, mitral stenosis)<br>Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies | Treat underlying heart disease | |
| **III. Pulmonary HTN due to Lung Disease and/or Hypoxia** | Parenchymal lung disease (COPD, interstitial fibrosis, cystic fibrosis)<br>Chronic alveolar hypoxia (chronic high altitude, alveolar hypoventilation disorders, sleep-disordered breathing) | Treat underlying cause of hypoxia and correct with supplemental oxygen (proven mortality benefit) | |
| **IV. Chronic Thromboembolic Pulmonary HTN (CTEPH)** | Thromboembolic obstruction of proximal pulmonary arteries<br>Obstruction of distal pulmonary arteries – PE (thrombus, foreign material, tumour, in situ thrombosis) | Anticoagulation, thromboendarterectomy, riociguat | |
| **V. Pulmonary HTN with Unclear Multifactorial Mechanisms** | Hematologic disorders (e.g. sickle cell)<br>Systemic disorders (e.g. sarcoidosis)<br>Metabolic disorders<br>Extrinsic compression of central pulmonary veins (tumour, adenopathy, fibrosing mediastinitis)<br>Chronic hemolytic anemia<br>Segmental pulmonary hypertension | Treat underlying cause | |

Adapted from: Simonneau G, et al. J Am Coll Cardio 2013:62(25 Suppl):D34-D41

## IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION (PRIMARY PULMONARY HYPERTENSION)

### Definition

- pulmonary HTN in the absence of a demonstrable cause
- histology includes medial hypertrophy, intimal fibrosis, and plexiform arteriopathy
- exclude:
  - left-sided cardiac valvular disease
  - myocardial disease
  - congenital heart disease
  - any clinically significant parenchymal lung disease
  - systemic connective-tissue disease
  - chronic thromboembolic disease

### Epidemiology

- usually presents in young females (20-40 yr); mean age of diagnosis is 36 yr
- most cases are sporadic; familial predisposition in 10% of cases, some linked to mutations in BMPR2
- may be associated with the use of anorexic drugs (e.g. Aminorex®, Fenfluramine®), amphetamines, and cocaine



**Guidelines for Vasodilator Response in Pulmonary Arterial HTN**

- Patients with idiopathic pulmonary arterial hypertension (IPAH) that respond to vasodilators acutely, have an improved survival with long-term use of CCBs
- Vasoreactivity testing: short-acting agent such as IV epoprostenol, IV adenosine, or inhaled NO
- Positive vasodilator response: mean pulmonary artery pressure (PAP) fall of at least 10 mmHg to ≤40 mmHg with an increased or unchanged cardiac output (European Society of Cardiology)
- Positive vasodilator response: should be considered as candidate for trial of oral CCB therapy

Medical Therapy for Pulmonary Arterial Hypertension. ACCP Evidence-Based Clinical Practice Guidelines. Chest 2004;(Suppl)06:126

### Signs and Symptoms

**Table 20. Signs and Symptoms of Pulmonary Hypertension**

| Symptoms | Signs |
|---|---|
| Dyspnea | Loud, palpable P2 |
| Fatigue | RV heave |
| Retrosternal chest pain | Right-sided S4 (due to RVH) |
| Syncope | Systolic murmur (tricuspid regurgitation [TR]) |
| Symptoms of underlying disease | If RV failure: right sided S3, increased JVP, positive HJR, peripheral edema, TR |
| | Reynaud's phenomenon |

Pulmonary arterial pressures are measured by pulmonary artery catheters (i.e. Swan-Ganz catheter) which are inserted into a large vein (often internal jugular). A balloon at the end of the catheter tip is inflated causing the catheter to advance through the right side of the heart and into the pulmonary artery. This allows for the measurement of RA, RV, PA, and pulmonary capillary wedge pressures as well as sampling of mixed venous blood. A thermistor near the end of the catheter also allows for assessment of cardiac output by thermodilution

### Investigations
- CXR: enlarged central pulmonary arteries, cardiac changes due to RV enlargement (filling of retrosternal air space)
- ECG: RVH/right-sided strain (see Cardiology and Cardiac Surgery, C34)
- 2-D echo doppler assessment of right ventricular systolic pressure
- cardiac catheterization: direct measurement of pulmonary artery pressures (necessary to confirm diagnosis)
- PFTs to assess for underlying lung disease: $DL_{CO}$ usually reduced; volumes and flows normal
- CT angiogram to assess lung parenchyma and possible PE
- V/Q scan ± pulmonary angiogram to rule out thromboembolic disease
- serology: ANA positive in 30% of patients with primary pulmonary HTN; other serologic markers can be used in the appropriate clinical setting

**Virchow's Triad**
- Venous stasis
- Endothelial cell damage
- Hypercoagulable states

### Treatment
- see Table 19

### Prognosis
- 2-3 yr mean survival from time of diagnosis
- survival decreases to approximately 1 yr if severe pulmonary HTN or right-heart failure

## Pulmonary Embolism

### Definition
- lodging of a blood clot in the pulmonary arterial tree with subsequent increase in pulmonary vascular resistance, impaired V/Q matching, and possibly reduced pulmonary blood flow

### Etiology and Pathophysiology
- one of the most common causes of preventable death in the hospital
- proximal leg thrombi (popliteal, femoral, or iliac veins) are the source of most clinically recognized pulmonary emboli
- thrombi often start in calf, but must propagate into proximal veins to create a sufficiently large thrombus for a clinically significant PE
- fewer than 30% of patients have clinical evidence of DVT (e.g. leg swelling, pain, or tenderness)
- always suspect PE if patient develops fever, sudden dyspnea, chest pain, or collapse 1-2 wk after surgery

### Risk Factors
- stasis
  - immobilization: paralysis, stroke, bed rest, prolonged sitting during travel, immobilization of an extremity after fracture
  - obesity, CHF
  - chronic venous insufficiency
- endothelial cell damage
  - post-operative injury, trauma
- hypercoagulable states
  - underlying malignancy (particularly adenocarcinoma)
  - cancer treatment (chemotherapy, hormonal)
  - exogenous estrogen administration (OCP, HRT)
  - pregnancy, post-partum
  - prior history of DVT/PE, family history
  - nephrotic syndrome
  - coagulopathies: Factor V Leiden, Prothrombin 20210A variant, inherited deficiencies of antithrombin/protein C/protein S, antiphospholipid antibody, hyperhomocysteinemia, increased Factor VIII levels, and myeloproliferative disease
- increasing age

**Multidetector Computed Tomography for Acute Pulmonary Embolism (PIOPED II Trial)**
NEJM 2006;354:2317-27
**Study**: Multicentre, prospective study investigating accuracy of computed tomography angiography (CTA) alone and combined with venous phase imaging (CTA-CTV) for the diagnosis of PE.
**Patients**: 824 patients of several thousand eligible for study received reference diagnosis to confirm absence or presence of PE (V/Q scan, venous compression U/S of lower extremities, and pulmonary digital-subtraction angiography (DSA) if necessary). To confirm absence, patients in whom PE was excluded were telephoned 3-6 mo after enrollment. Any deaths were reviewed by an outcome committee. All patients enrolled also underwent clinical assessment of PE (including a Wells' score) prior to imaging.
**Outcomes**: Diagnosis of pulmonary embolism.
**Results**: 773 of 824 patients had adequate CTAs for interpretation. PE was diagnosed in 192 of the 824 patients. Sensitivity was 83% (150 of 181 patients, 95% CI 0.76-0.92) and specificity was 96% (567 of 592 patients, 95% CI 0.93-0.97). However, the predictive value of CTA-CTV varied when clinical pre-test probability was taken into account. PPV of CTA for high, intermediate and low clinical probability were 96% (95% CI 0.78-0.99), 92% (95% CI 0.84-0.96), and 58% (95% CI 0.40-0.73), respectively. NPV of CTA for high, intermediate, and low clinical probability were 60% (95% CI 0.32-0.83), 89% (95% CI 0.82-0.93), and 96% (95% CI 0.92-0.98) respectively.
**Conclusion**: CTA is effective for diagnosing or excluding PE in accordance with assessment of clinical pretest probability. When clinical probability is inconsistent with imaging results, further investigations are required to rule out PE.

## Investigations (if highly suspicious, go straight to CT angiogram)

- see Emergency Medicine, ER33

### Table 21. Common Investigations for Pulmonary Embolism

| Investigation | Purpose/Utility |
|---|---|
| **Pulmonary Angiogram (Gold Standard)** | Filling defect indicative of embolus; negative angiogram excludes clinically relevant PE<br>More invasive, and harder to perform than CT, therefore done infrequently |
| **D-Dimer** | Highly sensitive D-dimer result can exclude DVT/PE if pretest probability is already low<br>Little value if pretest probability is high<br>If D-dimer positive, will need further evaluation with compression U/S (for DVT) and/or CT (for PE) |
| **CT Angiogram** | Both sensitive and specific for PE<br>Diagnosis and management uncertain for small filling defects<br>CT may identify an alternative diagnosis if PE is not present<br>CT scanning of the proximal leg and pelvic veins can be done at the same time and may be helpful |
| **Venous Duplex U/S or Doppler** | With leg symptoms<br>Positive test rules in proximal DVT<br>Negative test rules out proximal DVT<br>Without leg symptoms<br>Positive test rules in proximal DVT<br>Negative test does not rule out a DVT: patient may have non-occlusive or calf DVT |
| **ECG** | Findings not sensitive or specific<br>Sinus tachycardia most common; may see non-specific ST segment and T wave changes<br>RV strain, RAD, RBBB, S1-Q3-T3 with massive embolization |
| **CXR** | Frequently normal; no specific features<br>Atelectasis (subsegmental), elevation of a hemidiaphragm<br>Pleural effusion: usually small<br>Hampton's hump: cone-shaped area of peripheral opacification representing infarction<br>Westermark's sign: dilated proximal pulmonary artery with distal oligemia/decreased vascular markings (difficult to assess without prior films)<br>Dilatation of proximal PA: rare |
| **V/Q Scan** | Very sensitive but low specificity<br>Order scan if:<br>CXR normal, no COPD<br>Contraindication to CT (contrast allergy, renal dysfunction, pregnancy)<br>Avoid V/Q scan if:<br>CXR abnormal or COPD<br>Inpatient<br>Suspect massive PE<br>Results:<br>Normal: excludes the diagnosis of PE<br>High probability: most likely means PE present, unless pre-test probability is low<br>60% of V/Q scans are nondiagnostic |
| **Echocardiogram** | Useful to assess massive or chronic PE<br>Not routinely done |
| **ABG** | No diagnostic use in PE (insensitive and nonspecific)<br>May show respiratory alkalosis (due to hyperventilation) |

## Treatment

- admit for observation (stable patients with DVT only may be sent home on LMWH)
- oxygen: supplemental oxygen should be administered to target an oxygen saturation ≥90 percent
- pain relief: analgesics if chest pain – narcotics or acetaminophen
  - acute anticoagulation: therapeutic-dose SC LMWH or fondaparinux or unfractionated heparin or oral factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) or direct thrombin inhibitors (dabigatran) – start ASAP
  - anticoagulation stops clot propagation, prevents new clots, and allows endogenous fibrinolytic system to dissolve existing thromboemboli over months; get baseline CBC, INR, aPTT ± renal function ± liver function
  - for SC LMWH: dalteparin 200 U/kg once daily, enoxaparin 1 mg/kg bid, or fondaparinux 5-10 mg once daily – no lab monitoring – avoid or reduce dose in renal dysfunction
  - for IV heparin: bolus of 75 U/kg (usually 5000 U) followed by infusion starting at 20 U/kg/h – aim for aPTT 2-3x control
- long-term anticoagulation
  - for most non-pregnant patients who do not have renal insufficiency or active cancer, first-line is direct oral anticoagulants (rivaroxaban, apixaban, edoxaban, or dabigatran) rather than warfarin
  - warfarin: start the same day as LMWH/heparin – overlap warfarin with LMWH/heparin for at least 5 d and until INR in target range of 2-3 for at least 2 d (use for patients with severe renal insufficiency)
  - LMWH instead of warfarin for pregnancy, active cancer, or high bleeding risk patients
- IV thrombolytic therapy
  - if patient has massive PE (hypotension or clinical right heart failure) and no contraindications
  - hastens resolution of PE but may not improve survival or long-term outcome and doubles risk of major bleeding

D-dimer is elevated in patients with increased age, recent surgery, cancer, inflammation, infection, pregnancy, and severe renal dysfunction. It has good sensitivity and negative predictive value, but poor specificity and positive predictive value

Classic ECG finding of PE is S1-Q3-T3 (inverted T3), but most commonly see only sinus tachycardia

**Clinical Prediction Rule for Pulmonary Embolism**
J Thromb Hemost 2000;83:416-20
**Wells' Criteria**

| Risk Factors | Points |
|---|---|
| Clinical signs of DVT | 3.0 |
| No more likely alternative diagnosis (using H&P, CXR, ECG) | 3.0 |
| Immobilization or surgery in previous 4 wk | 1.5 |
| Previous PE/DVT | 1.5 |
| HR >100 beats/min | 1.5 |
| Hemoptysis | 1.0 |
| Malignancy | 1.0 |
| **Clinical Probability** | |
| Low (0-2) | 3% |
| Intermediate (3-6) | 28% |
| High (>6) | 78% |
| Modified Wells': >4 PE likely; ≤4 PE unlikely | |

JAMA 2006

**PE Rule Out Criteria (PERC)**
**Prospective Multicentre Evaluation of the Pulmonary Embolism Rule Out Criteria**
J Thromb Hemost 2008;6:772

- Age less than 50 yr
- Heart rate less than 100 bpm
- Oxyhemoglobin saturation ≥95 percent
- No hemoptysis
- No estrogen use
- No prior DVT or PE
- No unilateral leg swelling
- No surgery or trauma requiring hospitalization within the past 4 wk

Acute PE can probably be excluded without further diagnostic testing if the patient meets all PERC criteria AND there is a low clinical suspicion for PE, according to either the Wells' criteria or a low gestalt probability determined by the clinician prior to diagnostic testing for PE.

**Evaluation of a Suspected Pulmonary Embolism**
*Low clinical probability of embolism*
D-dimer (+ve) → CT scan (+ve) → ruled in
(–ve) → ruled out
Intermediate or high probability
CT scan (–ve) → ruled out
(+ve) → ruled in

Notes

- Use D-dimers only if low clinical probability, otherwise, go straight to CT
- If using V/Q scans (CT contrast allergy or renal failure):
- Negative V/Q scan rules out the diagnosis
- High probability V/Q scan only rules in the diagnosis if have high clinical suspicion
- Inconclusive V/Q scan requires leg U/S to look for DVT or CT

- interventional thrombolytic therapy
  - massive PE may be treated with catheter-directed thrombolysis by an interventional radiologist
  - catheter-directed thrombolysis is not recommended over systemic thrombolysis
- IVC filter: only if recent proximal DVT + absolute contraindication to anticoagulation
- duration of long-term anticoagulation: individualized, however generally
  - if reversible cause for PE (surgery, injury, pregnancy, etc.): 3-6 mo
  - if PE unprovoked: 6 mo to indefinite
  - if ongoing major risk factor (active cancer, antiphospholipid antibody, etc.): indefinite

### Thromboprophylaxis
- mandatory for most hospital patients: reduces DVT, PE, all-cause mortality, cost-effective
- start ASAP
- continue at least until discharge or recommend extending for 35 d post-operatively, if major orthopedic surgery

**Table 22. VTE Risk Categories and Prophylaxis (see Hematology, H37)**

| Risk Group | Prophylaxis Options |
|---|---|
| **Low Thrombosis Risk** | |
| Medical patients: fully mobile | No specific prophylaxis |
| Surgery: <30 min, fully mobile | Frequent ambulation |
| **Moderate Thrombosis Risk** | |
| Most general, gynecologic, urologic surgery | LMWH |
| Sick medical patients | Low dose unfractionated heparin |
| | Fondaparinux |
| **High Thrombosis Risk** | |
| Arthoplasty, hip fracture surgery | LMWH |
| Major trauma, spinal cord injury | Fondaparinux |
| | Warfarin (INR 2-3) |
| | Dabigatran |
| | Apixaban |
| | Rivaroxaban |
| | Low dose unfractionated heparin |
| **High Bleeding Risk** | |
| Neurosurgery, intracranial bleed | TED stockings™, pneumatic compression devices |
| Active bleeding | LMWH or low dose heparin when bleeding risk decreases |

**Workup for Idiopathic VTE**
Thrombophilia Workup: recurrent or idiopathic DVT/PE, age <50, FHx, unusual location, massive
Malignancy Workup: 12% of patients with idiopathic VTE will have a malignancy

**The Use of Unfractionated Heparin Should Be Limited to:**
- Patients with severe renal dysfunction (CrCl <30 ml/min) in whom LMWH and novel oral anticoagulation should be avoided
- Patients at elevated risk of bleeding that may need rapid reversal of anticoagulation
- Patients who receive thrombolytic therapy

**Extended Use of Dabigatran, Warfarin or Placebo in Venous Thromboembolism**
NEJM 2013;368:709-18
**Study**: Two double blind, RCTs; one comparing against placebo, the other against active treatment.
**Population**: 4199 patients (2856 in active-control study, 1343 in placebo-control study) with VTE who had completed at least 3 mo of therapy.
Intervention: In the active-control study, patients randomized to either 150 mg dabigatran or warfarin (INR 2.0-3.0). Patients in the placebo-control study received either 150 mg dabigatran or placebo.
**Outcome**: Recurrence of VTE, risk of major or clinically relevant bleed.
**Results**: In the active-control study, there was a hazard ratio (HR) of 1.44 (95% CI 0.78-2.64 for non-inferiority) of recurrent VTE with dabigatran vs. warfarin. HR of major or clinically relevant bleed was 0.54 (95% CI 0.41-0.71). In the placebo-control study, the HR of VTE with dabigatran vs. placebo was 0.08 (95% CI 0.02-0.25). HR of major or clinically relevant bleed was 2.92 (95% CI 1.52-5.60).
**Conclusions**: Dabigatran appears to be non-inferior to warfarin in the prevention of VTE recurrence. Dabigatran is associated with a lower risk of major or clinically relevant bleed than warfarin, but greater than placebo.

# Pulmonary Vasculitis

**Table 23. Pulmonary Vasculitis**

| Disease | Definition | Pulmonary Features | Extra-Pulmonary Features | Investigations | Treatment |
|---|---|---|---|---|---|
| **Granulomatosis with Polyangiitis (GPA, previously Wegener's Granulomatosis)** (see Nephrology, NP22) | Systemic vasculitis of medium and small arteries | Necrotizing granulomatous lesions of the upper and lower respiratory tract | Focal necrotizing lesions of arteries and veins; crescentic glomerulonephritis | CXR: nodules, cavities, and alveolar opacities<br>c-ANCA<br>Tissue confirmation | Corticosteroids and cyclophosphamide or rituximab |
| **Eosinophilic Granulomatosis with Polyangiitis (EGPA, Churg-Strauss)** | Multisystem disorder characterized by allergic rhinitis, asthma, and prominent peripheral eosinophilia | Asthma<br>Infiltrates | Life-threatening systemic vasculitis involving the lungs, pericardium and heart, kidneys, skin, and PNS (mononeuritis multiplex) | Peripheral eosinophilia is the most common finding<br>p-ANCA may be positive<br>Biopsy involved tissue | Corticosteroids |
| **Anti-GBM Disease (Goodpasture's)** (see Nephrology, NP22) | A disorder characterized by diffuse alveolar hemorrhage and glomerulonephritis caused by anti-GBM antibodies, which cross-react with basement membranes of the kidney and lung | Hemoptysis<br>May follow influenza infection | Anemia | CXR: may see alveolar infiltrates if hemorrhage is profuse<br>ELISA test with anti-GBM antibodies<br>Renal biopsy/indirect immunofluorescence shows linear staining | Acutely: corticosteroids, plasmapheresis, immunosuppressive therapy<br>Severe cases: bilateral nephrectomy |
| **Systemic Lupus Erythematosus, Rheumatoid Arthritis, Scleroderma** | See Rheumatology, RH18 | | | | |

# Pulmonary Edema

- see Cardiology and Cardiac Surgery, C35

Scleroderma is the most common collagen vascular disease affecting the lung

# Diseases of the Mediastinum and Pleura

## Mediastinal Masses

### Definition
- mediastinum: bound by the thoracic inlet, diaphragm, sternum, vertebral bodies, and the pleura
- can be broken down into 3 compartments: anterior, middle, and posterior

### Etiology and Pathophysiology
- diagnosis is aided by location and patient's age
- anterior compartment: more likely to be malignant
  - "Four Ts" (see sidebar), lymphoma, lipoma, pericardial cyst
- middle compartment
  - pericardial cyst, bronchogenic cyst/tumour, lymphoma, lymph node enlargement, aortic aneurysm
- posterior compartment
  - neurogenic tumours, meningocele, enteric cysts, lymphoma, diaphragmatic hernias, esophageal tumour, aortic aneurysm

**Horner's Syndrome**
Ptosis, Miosis, Anhydrosis

**Differential of an Anterior Compartment Mass**

**4 Ts**
**T**hymoma
**T**hyroid enlargement (goitre)
**T**eratoma
**T**umours (lymphoma, parathyroid, esophageal, angiomatous)

### Signs and Symptoms
- 50% asymptomatic (mainly benign); when symptomatic, 50% are malignant
- chest pain, cough, dyspnea, recurrent respiratory infections
- hoarseness, dysphagia, Horner's syndrome (see sidebar), facial/upper extremity edema (SVC compression)
- paraneoplastic syndromes (e.g. myasthenia gravis [thymomas])

### Investigations
- CXR (compare to previous)
- CT with contrast (anatomic location, density, relation to mediastinal vascular structures)
- MRI: specifically indicated in the evaluation of neurogenic tumours
- U/S (best for assessment of structures in close proximity to the heart and pericardium)
- radionuclide scanning: $^{131}$I (for thyroid), gallium (for lymphoma)
- biochemical studies: thyroid function, serum calcium, phosphate, PTH, AFP, β-hCG
- biopsy (mediastinoscopy, percutaneous needle aspiration)

**Mediastinal Components**
**Anterior**: sternum to pericardium and great vessels. Includes: thymus, extrapericardial aorta and branches, great veins, lymphatic tissues
**Middle**: pericardium (anteriorly), posterior pericardial reflection, diaphragm, thoracic inlet. Includes: heart, intrapericaridal great vessels, pericardium, trachea
**Posterior**: posterior pericardial reflection, posterior border of vertebral bodies, first rib to the diaphragm. Includes: esophagus, vagus nerve, thoracic duct, sympathetic chain, azygous venous system

### Management
- excision - symptomatic benign mass that is enlarging or a mass with concerns for malignancy
- resect bronchogenic cysts and localized neurogenic tumours via minimally invasive video assisted procedures
- exploration via sternotomy or thoracotomy
- diagnostic biopsy rather than major operation if mass is likely to be a lymphoma, germ cell tumour, or unresectable invasive malignancy
- ± post-operative radiotherapy/chemotherapy if malignant

## Mediastinitis

- most common causes: post-operative complications of cardiovascular or thoracic surgical procedures

### Acute
- etiology
  - complication of endoscopy (e.g. esophageal perforation providing entry point for infection)
  - esophageal or cardiac surgery
  - tumour necrosis
- signs and symptoms
  - fever, substernal pain
  - pneumomediastinum, mediastinal compression
  - Hamman's sign (auscultatory "crunch" during cardiac systole)
- treatment
  - antibiotics (IV vancomycin + 3rd gen cephalosporin), drainage, ± surgical closure of perforation

### Chronic
- usually granulomatous process or fibrosis related to previous infection (e.g. histoplasmosis, TB, sarcoidosis, syphilis)

# Pleural Effusions

## Definition
- excess amount of fluid in the pleural space (up to 25 mL normal amount)

## Etiology
- disruption of normal equilibrium between pleural fluid formation/entry and/or pleural fluid absorption/exit
- pleural effusions are classified as transudative or exudative
  - distinguish clinically using Light's Criteria (98% sensitivity and 83% specificity for identifying exudative pleural effusions)

**Starling's hypothesis**: The rate of passive fluid movement across a capillary wall is governed by the gradients of hydrostatic pressure and oncotic pressure across the same capillary wall

### Table 24. Laboratory Values in Exudative Pleural Effusion

| | Light's Criteria | Modified Light's Criteria |
|---|---|---|
| **Protein – Pleural/Serum** | >0.5 | >0.5 |
| **LDH – Pleural/Serum** | >0.6 | >0.6 |
| **Pleural LDH** | >2/3 upper limit of N serum LDH | >0.45 upper limit of N serum LDH |
| **Exudate = any one criterion** | | |

Ann Intern Med 1979;77:507-513 Chest 1997;111:970-980

All criteria for transudate must be fulfilled to be considered a transudative effusion. If any one of the criteria for exudates is met – it is an exudate

## Transudative Pleural Effusions
- pathophysiology: alterations to Starling forces affects the rates of formation and absorption of pleural fluid
- etiology
  - CHF: usually right-sided or bilateral
  - cirrhosis leading to hepatic hydrothorax
  - nephrotic syndrome, protein losing enteropathy, cirrhosis
  - pulmonary embolism (may cause transudative but more often causes exudative effusion)
  - peritoneal dialysis, hypothyroidism, CF, urinothorax

**Transudative** effusions are usually bilateral, not unilateral

**Exudative** effusions can be bilateral or unilateral

## Exudative Pleural Effusions
- pathophysiology: increased permeability of pleural capillaries or lymphatic dysfunction

### Table 25. Exudative Pleural Effusion Etiologies

| Etiology | Examples |
|---|---|
| **Infectious** | Parapneumonic effusion (associated with bacterial pneumonia, lung abscess) |
| | Empyema (bacterial, fungal, TB) |
| | TB pleuritis |
| | Viral infection |
| | Fungal |
| | Parasitic |
| **Malignancy** | Lung carcinoma (35%) |
| | Lymphoma (10%) |
| | Metastases: breast (25%), ovary, kidney |
| | Mesothelioma |
| | Myeloma |
| **Inflammatory** | Collagen vascular diseases: RA, SLE |
| | Pancreatitis |
| | Benign asbestos related effusion |
| | Pulmonary embolism |
| | ARMS |
| | Post-CABG or cardiac injury |
| | Drug reaction |
| **Intra-Abdominal** | Subphrenic abscess |
| | Pancreatic disease (elevated pleural fluid amylase) |
| | Meigs' syndrome (ascites and hydrothorax associated with an ovarian fibroma or other pelvic tumour) |
| **Intra-Thoracic** | Esophageal perforation (elevated fluid amylase) |
| **Trauma** | Hemothorax: rupture of a blood vessel, commonly by trauma or tumours |
| | Pneumothorax (spontaneous, traumatic, tension) |
| | Chylothorax |
| | Iatrogenic |
| **Other** | Drug-induced |
| | Hypothyroidism |

**Appearance of Pleural Fluid**
- Bloody: trauma, malignancy
- White: empyema, chylous, or chyliform effusion
- Black: aspergillosis, amoebic liver abscess
- Yellow-green: rheumatoid pleurisy
- Viscous: malignant mesothelioma
- Ammonia odour: urinothorax
- Food particles: esophageal rupture

### Signs and Symptoms
- often asymptomatic
- dyspnea: varies with size of effusion and underlying lung function
- orthopnea
- pleuritic chest pain
- inspection: trachea deviates away from effusion, ipsilateral decreased expansion
- percussion: decreased tactile fremitus, dullness
- auscultation: decreased breath sounds, bronchial breathing and egophony at above fluid level, pleural friction rub

### Investigations
- CXR
  - must have >200 mL of pleural fluid for visualization on PA film
  - lateral: >50 mL leads to blunting of posterior costophrenic angle
  - PA: blunting of lateral costophrenic angle
  - dense opacification of lung fields with concave meniscus
  - decubitus: fluid will layer out unless it is loculated
  - supine: fluid will appear as general haziness
- CT: helpful in differentiating parenchymal from pleural abnormalities, may identify underlying lung pathology
- U/S: detects small effusions and can guide thoracentesis
- thoracentesis: indicated if pleural effusion is a new finding; order blood work (LDH, glucose, protein) at the same time for comparison
  - risk of re-expansion pulmonary edema if >1.5 L of fluid is removed
  - inspect for colour, character, and odour of fluid
  - analyze fluid
- pleural biopsy: indicated if suspect TB, mesothelioma, or other malignancy (and if cytology negative)

**Role of CT in Pleural Effusion**
- To assess for fluid loculation, pleural thickening and nodules, parenchymal abnormalities, and adenopathy
- Helps to distinguish benign from malignant effusion and transudative from exudative effusion
- May not distinguish empyema from parapneumonic effusion

**Features of Malignant Effusion**
- Multiple pleural nodules

**Features of Exudative Effusion**
- Loculation
- Pleural thickening
- Pleural nodules
- Extrapleural fat of increased density

**Table 26. Analysis of Pleural Effusion**

| Measure | Purpose |
|---|---|
| **Protein, LDH** | Transudate vs. exudate |
| | LDH especially high (>1000 IU/L) in empyema, rheumatoid, malignancy |
| | Protein especially high in TB, myeloma |
| **Gram Stain, Ziehl-Nielsen Stain (TB), Culture** | Looking for specific organisms |
| **Cell Count Differential** | Neutrophils vs. lymphocytes (lymphocytic effusion in TB, cancer, lymphoma, serositis) |
| **Cytology** | Malignancy, infection |
| **Glucose** | Low (fluid:serum <0.5) in rheumatoid, TB, empyema, malignancy, esophageal rupture |
| **Rheumatoid Factor, ANA, Complement** | Collagen vascular disease |
| **Amylase** | Pancreatitis, esophageal perforation, malignancy |
| **pH** | Normally about 7.6 |
| | Very low (<7.0) in empyema, TB, rheumatoid, malignancy, esophageal rupture |
| **Blood** | Mostly traumatic, malignancy, PE with infarction, TB |
| **Triglycerides** | Chylothorax from thoracic duct leakage, mostly due to trauma, lung CA, or lymphoma |
| **Cholesterol** | Distinguish between chylous and chyliform effusion (seen in inflammation, e.g. TB, RA) |

**Pleural Effusions**

**Simple Effusion**
pH >7.2, LDH <1/2 serum, glucose >2.2

**Complicated Effusion**
pH <7.2, LDH >1/2 serum, glucose <2.2, positive Gram stain
Needs drainage

### Treatment
- thoracentesis
- treat underlying cause
- consider indwelling pleural catheter or pleurodesis in refractory effusions

When possible, organism-directed therapy, guided by culture sensitivities or local patterns of drug resistance, should be utilized

## Complicated Effusion
- see General Surgery and Thoracic Surgery, GS16

## Empyema
- see General Surgery and Thoracic Surgery, GS16

## Atelectasis
- see General Surgery and Thoracic Surgery, GS10

# Pneumothorax





- see General Surgery and Thoracic Surgery, GS17

**Need to Rule Out Life-Threatening Tension Pneumothorax**
**If pneumothorax with:**
- Severe respiratory distress
- Tracheal deviation to contralateral side
- Distended neck veins (↑ JVP)
- Hypotension

**Do not perform CXR**
**Needs immediate treatment**
See Emergency Medicine, ER11

# Asbestos-Related Pleural Disease and Mesothelioma

### Etiology and Pathophysiology
- benign manifestations of asbestos exposure:
  - benign asbestos pleural effusion
    - exudative effusion, typically ~10 yr after exposure, resolves
  - pleural plaques, usually calcified
    - marker of exposure; usually an asymptomatic radiologic finding
- mesothelioma
  - primary malignancy of the pleura
  - decades after asbestos exposure (even with limited exposure)
  - smoking not a risk factor, but asbestos and smoking synergistically increase risk of lung cancer

### Signs and Symptoms
- persistent chest pain, dyspnea, cough, bloody pleural effusion, weight loss

### Investigations
- biopsy (pleuroscopic or open)
- needle biopsy may seed needle tract with tumour

### Treatment
- resection (extrapleural pneumonectomy) requires careful patient selection; rarely successful (average survival <1 yr)

# Respiratory Failure



### Definition
- failure of respiratory system to maintain normal blood gases
- hypoxemic ($PaO_2$ <60 mmHg), hypercapnic ($PaCO_2$ >50 mmHg)
- acute vs. chronic (compensatory mechanisms activated)

### Signs and Symptoms
- signs of underlying disease
- hypoxemia: restlessness, confusion, cyanosis, coma, cor pulmonale
- hypercapnia: headache, dyspnea, drowsiness, asterixis, warm periphery, plethora, increased ICP (secondary to vasodilatation)

### Investigations
- serial ABGs
- CXR and/or CT, bronchoscopy to characterize underlying cause if unclear

# Hypoxemic Respiratory Failure

### Definition
- $PaO_2$ decreased, $PaCO_2$ normal or decreased

### Treatment
- reverse the underlying pathology
- oxygen therapy: maintain oxygenation (if shunt present, supplemental $O_2$ is less effective; see Anesthesia and Perioperative Medicine, A10, for oxygen delivery systems)
- ventilation, BiPAP, and PEEP/CPAP (see Anesthesia and Perioperative Medicine, A10): positive pressure can recruit alveoli and redistribute lung fluid
- improve cardiac output: ± hemodynamic support (fluids, vasopressors, inotropes), reduction of $O_2$ requirements

**Table 27. Approach to Hypoxemia**

| Type of Hypoxemia | Settings | $P_aCO_2$ | A-a$DO_2$ | Oxygen Therapy | Ventilation, BiPAP, and PEEP | Change in Cardiac Output |
|---|---|---|---|---|---|---|
| **1. Low $F_iO_2$** | Postop, high altitude | N or ↓ | N | Improves | No change | No change |
| **2. Hypoventilation** | Drug overdose | ↑ | N | Improves | Improves with ventilation | No change |
| **3a. Shunt (Intrapulmonary)** | ARDS, pneumonia | N or ↓ | ↑ | No change | Improves (except if one-sided) | Improves |
| **3b. Shunt (Right to Left)** | Pulmonary HTN | N or ↓ | ↑ | No change | Worsens | Worsens |
| **4. Low Mixed Venous $O_2$ Content** | Shock | ↓ | ↑ | Improves or no change | Worsens | Improves |
| **5. V/Q Mismatch** | COPD | N or ↑ | ↑ | Improves (small amounts) | Often improves | Improves |
| **6. Diffusion Impairment** | ILD, emphysema | N | ↑ | Improves | Improves with positive pressure | No change or worsens |

Reprinted with permission from Dr. Ian Fraser *Where "N" = within normal limits

# Hypercapnic Respiratory Failure

## Definition
- $PaCO_2$ increased, $PaO_2$ decreased

## Pathophysiology
- increased $CO_2$ production: fever, sepsis, seizure, acidosis, carbohydrate load
- alveolar hypoventilation: COPD, asthma, CF, chest wall disorder, dead space ventilation (rapid shallow breathing)
  - inefficient gas exchange results in inadequate $CO_2$ removal in spite of normal or increased minute volume
- hypoventilation
  - central: brainstem stroke, hypothyroidism, severe metabolic alkalosis, drugs (opiates, benzodiazepines)
  - neuromuscular: myasthenia gravis, Guillain-Barré, phrenic nerve injury, muscular dystrophy, polymyositis, kyphoscoliosis
  - muscle fatigue

## Treatment
- reverse the underlying pathology
- if $PaCO_2$ >50 mmHg and pH <7.35 consider noninvasive or mechanical ventilation
- correct exacerbating factors
  - NTT/ETT suction: clearance of secretions
  - bronchodilators: reduction of airway resistance
  - antibiotics: treatment of infections
  - reverse medications that may be contributing (e.g. narcotics)
- maintain oxygenation (see above)
- diet: increased carbohydrates can increase $PaCO_2$ in those with mechanical or limited alveolar ventilation; high lipids decrease $PaCO_2$

**Dead Space**
- Ventilation without perfusion
- The opposite of shunt

**Causes of Hypercapnia**
- High inspired $CO_2$
- Low total ventilation
- High deadspace ventilation
- High $CO_2$ production

In chronic hypercapnia, supplemental $O_2$ may decrease the hypoxic drive to breathe, but do not deny oxygen if the patient is hypoxic

In COPD patients with chronic hypercapnia ("$CO_2$ retainers"), provide supplemental oxygen to achieve target $SaO_2$ from 88-92%

# Acute Respiratory Distress Syndrome

## Definition
- clinical syndrome characterized by severe respiratory distress, hypoxemia, and noncardiogenic pulmonary edema
- The Berlin Criteria (JAMA 2012;307:2526-2533) for ARDS
  - acute onset
    - within 7 d of a defined event, such as sepsis, pneumonia, or patient noticing worsening of respiratory symptoms
      - usually occurs within 72 h of presumed trigger
    - bilateral opacities consistent with pulmonary edema on either CT or CXR
    - not fully explained by cardiac failure/fluid overload, but patient may have concurrent heart failure
    - objective assessment of cardiac function (e.g. echocardiogram) should be performed even if no clear risk factors

## Etiology
- direct lung injury
  - airway: aspiration (**gastric contents**, drowning), **pneumonia**, inhalation injury (oxygen toxicity, nitrogen dioxide, smoke)
  - circulation: embolism (fat, amniotic fluid), reperfusion injury

**ALI vs. ARDS:** Definition is the same, except ALI is a $P_aO_2/F_iO_2 \leq 300$, while ARDS is a $P_aO_2/F_iO_2 \leq 200$

**Categorization of ARDS as Mild, Moderate or Severe – The Berlin Criteria**

| ARDS Severity | $P_aO_2/FiO_2$ (mmHg)* | Mortality (95% CI) |
|---|---|---|
| Mild | 200-300 | 27 (24-30)% |
| Moderate | 100-200 | 32 (29-34)% |
| Severe | <100 | 45 (42-48)% |

*on ≥5 cm $H_2O$ PEEP, #P<0.001
JAMA 2012;307:2526-33

- indirect lung injury
  - circulation: **sepsis, shock, trauma**, blood transfusion, pancreatitis
  - neurogenic: head trauma, intracranial hemorrhage, drug overdose (narcotics, sedatives, TCAs)

### Pathophysiology
- disruption of alveolar capillary membranes → leaky capillaries → interstitial and alveolar pulmonary edema → reduced compliance, V/Q mismatch, shunt, hypoxemia, pulmonary HTN

### Clinical Course
**A. Exudative Phase**
- first 7 d of illness after exposure to ARDS precipitant
- alveolar capillary endothelial cells and type I pneumocytes are injured, resulting in loss of normally tight alveolar barrier
- patients develop dyspnea, tachypnea, increased work of breathing
  - these result in respiratory fatigue and eventually respiratory failure (see *Hypoxemic Respiratory Failure*, R25)

**B. Fibroproliferative Phase**
- after day 7
- may still experience dyspnea, tachypnea, fatigue, and hypoxemia
- most patients clinically improve and are able to wean off mechanical ventilation
- some patients develop fibrotic lung changes that may require long-term support on supplemental oxygen or even mechanical ventilation
- if fibrosis present, associated with increased mortality

### Treatment
- based on ARDS Network (see *Landmark Respirology Trials*, R34)
- treat underlying disorder (e.g. antibiotics if infection present)
- mechanical ventilation using low tidal volumes (<6 mL/kg) to prevent barotrauma
  - use optimal amount of PEEP to keep airways open and allow the use of lower $F_iO_2$
  - may consider using prone ventilation, ± inhaled nitric oxide, short term paralytics (<48 h) or ECMO (extracorpeal membrane oxygenation) if conventional treatment is failing
- fluids and inotropic therapy (e.g. dopamine, vasopressin) if cardiac output inadequate
- pulmonary-arterial catheter now seldom used for monitoring hemodynamics
- mortality: 30-40%, usually due to non-pulmonary complications
- sequelae of ARDS include residual pulmonary impairment, severe debilitation, polyneuropathy and psychologic difficulties, which gradually improve over time
- most survivors eventually regain near-normal lung function, often with mildly reduced diffusion capacity

**Risk Factors for Aspiration Pneumonia**

| Categories | Examples |
|---|---|
| Decreased level of consciousness | Alcoholism |
| Upper GI tract disorders | Dysphagia, esophageal disorders |
| Mechanical instrumentation | Intubation, nasogastric tube, feeding tube |
| Neurologic conditions | Dementia, Parkinson disease |
| Others | Protracted vomiting |

# Neoplasms

## Lung Cancer

- see General Surgery and Thoracic Surgery, GS18

## Approach to the Solitary Pulmonary Nodule

- see Medical Imaging, MI7
- see General Surgery and Thoracic Surgery, GS18

# Sleep-Related Breathing Disorders

## Hypoventilation Syndromes

- primary alveolar hypoventilation: idiopathic
- obesity-hypoventilation syndrome (Pickwickian syndrome)
- respiratory neuromuscular disorders

**Normal Respiratory Changes during Sleep**
- Tidal volume decreases
- Arterial $CO_2$ increases (due to decreased minute ventilation)
- Pharyngeal dilator muscles relax causing increased upper airway resistance

## Sleep Apnea

**Apnea**: absence of breathing for ≥10 s
**Hypopnea**: excessive decrease in rate or depth of breathing (>50% reduction in ventilation for >10 sec)
**Hyperpnea**: excessive increase in rate or depth of breathing

### Definition
- episodic decreases in airflow during sleep
- quantitatively measured by the Apnea/Hypopnea Index (AHI) = # of apneic and hypopneic events per hour of sleep
- sleep apnea generally accepted to be present if AHI ≥5
  - AHI: Mild OSA 5-15 events/h, Moderate 15-30 events/h, Severe >30 events/h

### Classification
- obstructive (OSA)
  - caused by transient, episodic obstruction of the upper airway
  - absent or reduced airflow despite persistent respiratory effort
- central (CSA) (see Neurology, N47)
  - can be hypercapneic CSA caused by transient, episodic decreases in CNS drive to breathe or nonhypercapnic where the drive to breathe is increased
  - no airflow because no respiratory effort
- Cheyne-Stokes Respiration: a form of CSA in which central apneas alternate with hyperpneas to produce a crescendo-decrescendo pattern of tidal volume; seen in severe LV dysfunction, brain injury, and other settings (see Figure 2)
- mixed (MSA)
  - features of both CSA and OSA
  - loss of hypoxic and hypercapnic drives to breathe secondary to "resuscitative breathing": overcompensatory hyperventilation upon awakening from OSA induced hypoxia

### Risk Factors
- for OSA: obesity, upper airway abnormality, neuromuscular disease, hypothyroidism, alcohol/sedative use, nasal congestion, sleep deprivation, enlarged tonsils, crowded oropharynx, short/wide neck
- for CSA: LV failure, brainstem lesions, stroke, brain tumours, encephalitis, encephalopathy, obesity (hypoventilation), neuromuscular disease, myxedema, high altitude, narcotics

### Signs and Symptoms
- obtain history from spouse/partner
- secondary to repeated arousals and fragmentation of sleep: nocturnal gasping/choking, daytime somnolence, personality and cognitive changes, snoring
- secondary to hypoxemia and hypercapnia: morning headache, polycythemia, pulmonary/systemic HTN, cor pulmonale/CHF, nocturnal angina, arrhythmias
- a typical presentation for OSA is a middle-aged obese male who snores

### Investigations
- sleep study (polysomnography)
- evaluates sleep stages, (EEG, EOG, EMG), airflow, ribcage movement, arousals, ECG, $SaO_2$, limb movements, snoring, body position, video recording
- indications
  - excessive daytime sleepiness
  - unexplained pulmonary HTN or polycythemia
  - daytime hypercapnia
  - titration of optimal nasal CPAP or BiPAP
  - assessment of objective response to other interventions (e.g. oral appliances for sleep apnea, positional therapy)

**Continuous Positive Airways Pressure for Obstructive Sleep Apnea**
Cochrane DB Syst Rev 2006;CD001106
**Study**: Pooled analysis of 36 RCTs (n=1718) comparing nocturnal CPAP with an inactive control or oral appliances in adults with OSA.
**Conclusions**: The use of CPAP showed significant improvements in objective and subjective measures including cognitive function, sleepiness, measures of quality of life, and a lower average systolic and diastolic blood pressure. People who responded equally well to CPAP and oral appliances expressed a strong preference for oral appliances; however, participants on oral appliances were more likely to withdraw from therapy.

### Treatment
- modifiable factors: weight loss, decreased alcohol/sedatives, nasal decongestion, treatment of underlying medical conditions
- OSA or MSA: nasal CPAP, postural therapy (e.g. no supine sleeping), dental appliance
- CSA or hypoventilation syndromes: nasal BiPAP/CPAP, respiratory stimulants (e.g. acetazolamide, theophylline, progesterone), adaptive servoventilation (e.g. progesterone) in select cases
- tracheostomy rarely required and should be used as last resort for OSA

CPAP has been shown to reduce cardiovascular risk and cardiovascular related deaths in patients with obstructive sleep apnea

### Complications
- depression, weight gain, decreased quality of life, workplace and vehicular accidents, cardiac complications (e.g. HTN), reduced work/social function
- associated with higher potential risk of CVS complications (e.g. heart attacks, strokes, arrhythmias, heart failure)

# Introduction to Intensive Care

## Intensive Care Unit Basics

- goal is to stabilize critically ill patients: hemodynamic, respiratory, or cardiac instability, or need for close monitoring

## Lines and Catheters

- arterial lines
  - monitor beat-to-beat blood pressure variations, obtain blood for routine ABGs
  - common sites are the radial and femoral arteries
- central venous catheter (central line)
  - administer IV fluids, monitor CVP, insert pulmonary artery catheters
  - administer TPN and agents too irritating for peripheral line (e.g. vasopressors, chemotherapy)
  - common sites: internal jugular vein, subclavian vein, femoral vein
- pulmonary arterial catheter
  - balloon guides the catheter from a major vein to the right heart
  - measures pulmonary capillary wedge pressure (PCWP) via a catheter wedged in distal pulmonary artery
  - PCWP reflects the LA and LV diastolic pressure (barring pulmonary venous or mitral valve disease)
  - indications (now used infrequently due to associated complications)
    - diagnosis of shock, primary pulmonary HTN, valvular disease, intracardiac shunts, cardiac tamponade, PE
    - assessment of hemodynamic response to therapies
    - differentiation of high- versus low-pressure pulmonary edema
    - management of complicated MI, multiorgan system failure and/or severe burns, or hemodynamic instability after cardiac surgery
  - absolute contraindications
    - tricuspid or pulmonary valve mechanical prosthesis
    - right heart mass (thrombus or tumour)
    - tricuspid or pulmonary valve endocarditis

**Intensive vs. Conventional Glucose Control in Critically Ill Patients**
NEJM 2009;360:1283-97
**Purpose**: To assess whether intensive glucose control improves mortality in critically ill patients.
**Study**: Prospective, randomized controlled trial.
**Population**: 6104 patients expected to require ICU treatment for 3 or more consecutive days.
**Intervention**: Patients were randomized to insulin therapy regimens with intensive (blood glucose 4.5-6 mM) or conventional (blood glucose 10 mM or less) glucose control targets. Intravenous insulin therapy was used to maintain blood glucose in target range.
**Primary Outcome**: Death from any cause within 90 d after randomization.
**Results**: The odds ratio for death in the intensive control group was 1.14 (95% CI 1.02-1.28; P=0.02) and this effect did not differ between surgical and medical patients. Severe hypoglycemia (blood glucose <2.2 mM) was significantly more common in the intensive management group (6.8% versus 0.5%; P<0.001).
**Conclusion**: Intensive insulin therapy in ICU patients increased mortality compared to blood glucose targeting of less than 10 mM with a number needed to harm of 38.

**Table 28. Useful Equations and Cardiopulmonary Parameters**

| | |
|---|---|
| BSA = [Ht (cm) + Wt (kg) – 60]/100 | PCWP = LVEDP |
| SV = CO / HR | SVI = CI / HR |
| CI = CO / BSA | RV Ejection Fraction = SV / RVEDV |
| SVRI = [(MAP – RAP) 80]/CI | PP = sBP – dBP |
| P:F ratio = $P_aO_2$ / $F_iO_2$ | MAP = 1/3 sBP + 2/3 dBP = dBP + 1/3 PP |

BSA = body surface area; CI = cardiac index; CO = cardiac output; dBP = diastolic blood pressure; HR = heart rate; LVEDP = left ventricular end diastolic pressure; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; PP = pulse pressure; RAP = right atrial pressure; RVEDV = right ventricular end diastolic volume; sBP = systolic blood pressure; SV = stroke volume; SVI = stroke volume index; SVRI = systemic vascular resistance index

## Organ Failure

**Table 29. Types of Organ Failure**

| Type of Failure | Clinical Feature | Treatment |
|---|---|---|
| **Respiratory Failure** (see *Respiratory Failure*, R25) | Hypoxemia<br>Hypercapnia | Treat underlying cause (e.g. lung disease, shunt, V/Q mismatch, drug-related, cardiac)<br>Manage mechanical ventilation settings<br>Supplemental oxygen |
| **Cardiac Failure** (see Cardiology and Cardiac Surgery, C34) | Hypotension<br>Decreased urine output<br>Altered mental status<br>Arrhythmia<br>Hypoxia | Treat underlying cause (e.g. bradycardia, tachycardia, blood loss, adrenal insufficiency)<br>Volume resuscitation<br>Vasopressors<br>Inotropes<br>Intra-aortic balloon pump |
| **Coagulopathy** (see Hematology, H27, H31, H33) | Increased INR or PTT<br>Low platelet count<br>Bleeding, bruising | Treat underlying cause (e.g. thrombocytopenia, drug-related, immune-related, DIC)<br>Transfusion of blood products, clotting factors |
| **Liver Failure** (see Gastroenterology, G38) | Elevated transaminases, bilirubin<br>Coagulopathy<br>Jaundice<br>Altered mental status (encephalopathy)<br>Hypoglycemia | Treat underlying cause (e.g. viral hepatitis, drug related, metabolic)<br>Lactulose<br>Liver transplant |
| **Renal Failure** (see Nephrology, NP37) | Elevated creatinine<br>Reduced urine output<br>Signs of volume overload (e.g. CHF, effusions) | Treat underlying cause (e.g. shock, drug-related, obstruction)<br>Correct volume and electrolyte status, eliminate toxins<br>Diuretics<br>Dialysis |

# Shock

- see Emergency Medicine, ER3
- inadequate tissue perfusion potentially resulting in end organ injury
  - categories of shock
    - hypovolemic: hemorrhage, dehydration, vomiting, diarrhea, interstitial fluid redistribution
    - cardiogenic: myopathic (myocardial ischemia ± infarction), mechanical, arrhythmic, pharmacologic
    - obstructive: massive PE (saddle embolus), pericardial tamponade, constrictive pericarditis, increased intrathoracic pressure (e.g. tension pneumothorax)
    - distributive: sepsis, anaphylaxis, neurogenic, endocrine, toxins

**Causes of SHOCK**
**S**pinal (neurogenic), **S**eptic
**H**emorrhagic
**O**bstructive (e.g. tension pneumothorax, cardiac tamponade, PE)
**C**ardiogenic (e.g. arrhythmia, MI)
Anaphyla**K**tic

**Table 30. Changes Seen in Different Classes of Shock**

| | Hypovolemic | Cardiogenic | Obstructive | Distributive |
|---|---|---|---|---|
| **HR** | ↑ | ↑, N, or ↓ | ↑ | ↑ or ↓ |
| **BP** | ↓ | ↓ | ↓ | ↓ |
| **JVP** | ↓ | ↑ | ↑ | ↓ |
| **Extremities** | Cold | Cold | N or Cold | Warm |
| **Other** | Look for visible hemorrhage or signs of dehydration | Bilateral crackles on chest exam | Depending on cause, may see pulsus paradoxus, Kussmaul's sign, or tracheal deviation | Look for obvious signs of infection or anaphylaxis |

**Shock: Clinical Correlation**
**Hypovolemic**: patients have cool extremities due to peripheral vasoconstriction
**Cardiogenic**: patients usually have signs of left-sided heart failure
**Obstructive**: varied presentation
**Distributive**: patients have warm extremities due to peripheral vasodilation

- treat underlying cause (hypovolemia is the most common cause)
- treatment goal is to return critical organ perfusion to normal (e.g. normalize BP)
- common treatment modalities include:
  - fluid resuscitation (NOT in cardiogenic shock)
  - inotropes (e.g. dobutamine), vasopressors (e.g. norepinephrine), vasopressin
  - revascularization or thrombolytics for ischemic events
  - needle decompression or tube thoracostomy for suspected tension pneumothorax

# Sepsis

- the leading cause of death in noncoronary ICU settings is multi-organ failure due to sepsis
- the predominant theory is that sepsis is attributable to uncontrollable immune system activation

## Definitions

- sepsis: life threatening organ dysfunction caused by dysregulated host response to infection (Table 31)
- septic shock: a subset of sepsis, where sufficient circulatory and/or cellular/metabolic abnormalities substantially increase mortality. Clinically defined as sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mmHg and having a serum lactate ≥2 mmol/L (18 mg/dL) despite adequate fluid resuscitation

**Systemic Inflammatory Response Syndrome (SIRS):** generalized inflammatory reaction caused by infectious and noninfectious entities, manifested by two or more of:
- Body temperature >38°C or <36°C
- Heart rate >90/min
- Respiratory rate >20/min or $P_aCO_2$ <32 mmHg
- WBC >12,000 cells/mL or <4000 cells/mL or >10% bands

## Signs and Symptoms

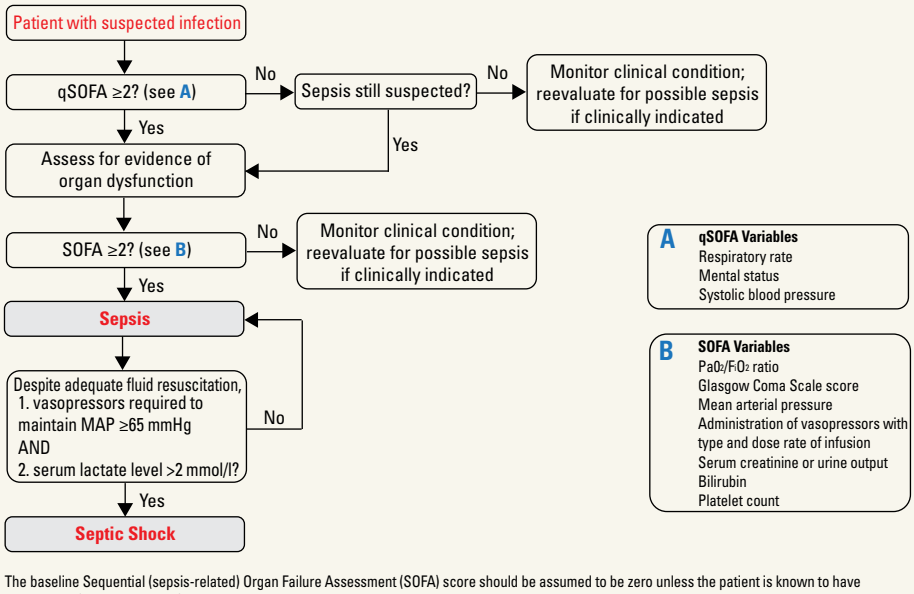
- new guidelines recommend the use of quick SOFA (qSOFA) criteria and SOFA score to replace SIRS criteria
- in patients with suspected infection, bedside application of qSOFA criteria identifies individuals with high likelihood of poor outcomes, including prolonged ICU stay and/or death
- a positive qSOFA (≥2 criteria) should prompt application of the SOFA score, and further evaluation of possible infection and organ dysfunction
- in the context of suspected infection, a SOFA score ≥2 reflects an overall mortality risk of 10%
- the absence of ≥2 criteria on either qSOFA or SOFA score should not delay or defer investigation or treatment of infection or any other aspect of care deemed necessary by the practitioners

**Quick SOFA (qSOFA) Criteria**
- Respiratory rate ≥22/min
- Altered mentation
- Systolic blood pressure ≤100 mmHg

**Table 31. Sequential (Sepsis-Related) Organ Failure Assessment (SOFA) Score**

| | Score | | | | |
|---|---|---|---|---|---|
| **System** | **0** | **1** | **2** | **3** | **4** |
| **Respiratory** | | | | | |
| $PaO_2/FiO_2$, mmHg (kPa) | ≥400 (53.3) | <400 (53.3) | <300 (40) | <200 (26.7) with respiratory support | <100 (13.3) with respiratory support |
| **Coagulation** | | | | | |
| Platelets, x103/μL | ≥150 | <150 | <100 | <50 | <20 |
| **Liver** | | | | | |
| Bilirubin, μmol/L (mg/dL) | <20 (1.2) | 20-32 (1.2-1.9) | 33-101 (2.0-5.9) | 102-204 (6.0-11.9) | >204 (12.0) |
| **Cardiovascular** | MAP ≥70 mmHg | MAP <70 mmHg | Dopamine <5a or dobutamine (any dose)[a] | Dopamine 5.1-15a or epinephrine <0.1a or norepinephrine <0.1a | Dopamine >15a or epinephrine >0.1a or norepinephrine >0.1a |
| **Central Nervous System** | | | | | |
| Glasgow coma scale score | 15 | 13-14 | 10-12 | 6-9 | <6 |
| **Renal** | | | | | |
| Creatinine, μmol/L (mg/dL) | <110 (1.2) | 110-170 (1.2-1.9) | 171-299 (2.0-3.4) | 300-440 (3.5-4.9) | >440 (5.0) |
| Urine output, mL/d | | | | <500 | <200 |

[a]Catecholamine doses are given as μg/kg/min for at least 1hr
Table adapted from Singer et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315(8): 801-810




The baseline Sequential (sepsis-related) Organ Failure Assessment (SOFA) score should be assumed to be zero unless the patient is known to have pre-existing (acute or chronic) organ dysfunction before the onset of infection. qSOFA indicated quick SOFA; MAP, mean arterial pressure.

**Figure 11. Approach to sepsis**
Figure adapted from Singer et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315(8): 801-810.

**Goal-Directed Resuscitation for Patients with Early Septic Shock**
NEJM 2014: 371;1496-06
**Study**: Prospective, randomized controlled trial.
**Population**: 1600 patients in Australia and New Zealand presenting to the emergency department with early septic shock.
**Intervention**: patients were randomized to receive early goal-directed therapy (EGDT) or usual care.
**Outcome**: The primary outcome was all-cause mortality within 90 d of randomization.
**Results**: The rate of death did not significantly differ between patients treated with EGDT or usual care (absolute risk difference EGDT versus usual care = -0.3%, 95% CI -4.1 to 3.6%; P=0.90). EGDT treated patients received more intravenous fluids, vasopressor infusions, red blood cell transfusions, and dobutamine (P<0.0001 for all). Survival time, in-hospital mortality, duration of organ support, and length of hospital stay did not significantly differ between patients randomized to EGDT or usual care.
**Conclusions**: EGDT did not improve all-cause mortality at 90 d in patients presenting to the emergency department with early septic shock.

**Corticosteroids for Treating Sepsis**
Cochrane DB Syst Rev 2015; CD002243
**Objectives**: Determine effects of corticosteroids on death at 1 mo in patients with sepsis.
**Methods**: RCTs in the Central Register of Controlled Trials, MEDLINE, and Latin American Caribbean Health Sciences Literature comparing corticosteroids vs. placebo or supportive treatment in patients with sepsis.
**Results**: 33 trials, 4268 participants. Corticosteroids reduced 28 d mortality (RR 0.87, 95% CI 0.76-1.00). Corticosteroids increased proportion of shock reversal by 7 d (RR 1.31, 95% CI 1.14-1.51) and 28 (RR 1.11, 95% CI 1.02-1.21) and reduced survivors' length of stay in ICU (MD -2.19, 95% CI -3.93- -0.46). Corticosteroids did not induce gastroduodenal bleeding, superinfection or neuromuscular weakness by did increase risk of hyperglycemia and hypernatremia.
**Conclusions**: Corticosteroids reduce mortality among patients with sepsis.

## Treatment

- identify the cause and source of infection: blood, sputum, urine Gram stain, and C&S
- initiate empiric antibiotic therapy
- monitor, restore, and maintain hemodynamic function

## Surviving Sepsis (adapted from International Guidelines for Management of Severe Sepsis and Septic Shock 2012)

- adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with demand
- initial resuscitation (goals during first 6 h of resuscitation for sepsis induced hypotension persisting after initial fluid challenge or blood lactate ≥4 mmol/L)
- maintain CVP 8-12 mmHg with IV crystalloids/colloids
  - maintain MAP ≥65 mmHg with use of vasopressor agents, first line: norepinephrine
  - urine output ≥0.5 mL/kg/hr
  - central venous (SVC) or mixed oxygen saturation 70% or 65% respectively
  - in patients with elevated lactate levels target resuscitation to normalize lactate
  - corticosteroid replacement therapy not indicated if adequate hemodynamic stability achieved with fluid resuscitation and vasopressor therapy

- infection control
  - prompt diagnosis of infection
    - cultures as clinically indicated prior to antibiotic therapy if no significant delay
    - imaging studies performed promptly to confirm possible infectious source
  - antibiotic therapy
- administer effective IV antimicrobials within first hour of recognition of sepsis
  - choice of anti-infective therapy should consider activity against all likely pathogens and penetrance of adequate concentration into tissue presumed to be source of infection
  - antimicrobial regimen should be reassessed daily for potential deescalation
- surgical source control when appropriate
- supportive oxygenation and ventilation using lung-protective regimen
- early nutritional support: enteral route is used to preserve function of intestinal mucosal barrier
- DVT/PE prophylaxis
- advanced care planning, including the communication of likely outcome and realistic goals of treatment with patients and families

# Common Medications

**Table 32. Common Medications for Respiratory Diseases**

| | Drug | Typical Adult Dose | Indications | Side Effects |
|---|---|---|---|---|
| **β2-AGONISTS** | | | | |
| **Short-Acting** | salbutamol/albuterol (Ventolin®, Airomir®) (light blue/navy MDI or diskus)<br>terbutaline (Bricanyl®) (blue turbuhaler) | 1-2 puffs q4-6h prn | Bronchodilator in acute reversible airway obstruction | CV (angina, flushing, palpitations, tachycardia, can precipitate atrial fibrillation), CNS (dizziness, H/A, insomnia, anxiety), GI (diarrhea, N/V), rash, hypokalemia, paroxysmal bronchospasm |
| **Long-Acting** | salmeterol (Serevent®) (green diskus), formoterol (Oxeze®, Foradil®) (blue/green turbuhalor or aerolizer) indacaterol (Onbrez®) (blue/white breezhaler) | 1-2 puffs bid<br>1 puff daily | Maintenance treatment (prevention of bronchospasm) in COPD, asthma | |
| **Combination Long-Acting β2- Agonist and Inhaled Corticosteroid** | fluticasone and salmeterol (Advair®) (purple MDI or diskus)<br>budesonide and formoterol (Symbicort®) (red turbuhaler)<br>Mometasone and formoterol (Zenhale®) (blue MDI) | 1 puff bid<br>2 puffs bid | COPD and asthma | Common: CNS, H/A, dizziness<br>Resp: URTI, GI (N/V, diarrhea, pain/discomfort, oral candidiasis) |
| **Combination Short-Acting β2- Agonist and Short-Acting Anti-Cholinergic** | ipratropium/salbutamol (Combivent®, Respimat®) (orange respimat) | 1 puff qid | Bronchodilator used in COPD | Palpitations, anxiety, dizziness, fatigue, H/A, N/V, dry mucous membranes, urinary retention, increased toxicity in combination with other anticholinergic drugs |
| **Combination Long-Acting β2- Agonist and Long-Acting Anti-Cholinergic** | umeclidinium/vilanterol (Anoro®) (red ellipta)<br>aclidinium/formoterol (Duaklir®) (yellow genuair)<br>tiotropium/olodaterol (Inspiolto®) (green respimat)<br>indacaterol/glycopyrronium (Ultibro®) (yellow breezhaler) | 1 puff daily<br>1 puff bid<br>1 puff daily<br>1 puff daily | Bronchodilator used in COPD | Palpitations, anxiety, dizziness, fatigue, H/A, N/V, dry mucous membranes, urinary retention, increased toxicity in combination with other anticholinergic drugs |
| **ANTICHOLINERGICS** | | | | |
| **Short-Acting Anti-Cholinergic** | ipratropium bromide (Atrovent®) (clear/green MDI) | 2-3 puffs qid | Bronchodilator used in asthma and COPD | Palpitations, anxiety, dizziness, fatigue, H/A, N/V, dry mucous membranes, urinary retention, increased toxicity in combination with other anticholinergic drugs |
| **Long-Acting Anti-Cholinergic** | tiotropium bromide (Spiriva®) (green handihaler or respimat)<br>glycopyrronium bromide (Seebri®) (orange breezhaler), umeclidinium (Incruse™) (green ellipta), aclidinium (Genuair®, Tudorza®) (green inhaler) | 1 puff qam<br>1 puff daily | Bronchodilator used in asthma and COPD | Palpitations, anxiety, dizziness, fatigue, H/A, N/V, dry mucous membranes, urinary retention, increased toxicity in combination with other anticholinergic drug |

**Table 32. Common Medications for Respiratory Diseases** (continued)

| | Drug | Typical Adult Dose | Indications | Side Effects |
|---|---|---|---|---|
| **CORTICOSTEROIDS** | | | | |
| **Inhaled** | fluticasone (Flovent®) (orange/peach MDI or diskus)<br>budesonide (Pulmicort®) (brown turbuhaler)<br>ciclesonide (Alvesco®) (red MDI)<br>beclomethasone (QVAR®, Vanceril®) (brown MDI)<br>mometasone (Asmanex®) (pink/grey/brown twisthaler)<br>fluticasone furoate (Arnuity®) (orange ellipta) | 2-4 puffs bid<br>2 puffs bid<br>1 puff daily or bid<br>1-4 puffs bid<br>1 puff daily or bid<br>1 puff daily | Maintenance treatment of asthma | H/A, fever, N/V, MSK pain, URTI, throat irritation, growth velocity reduction in children/adolescents, HPA axis suppression, increased pneumonia risk in COPD |
| **Systemic** | prednisone (Apo-prednisone®, Deltasone®)<br>methylprednisolone (Depo-Medrol®, Solu-Medrol®) | Typically 40-60 mg/d PO<br>125 mg q8h IV (sodium succinate) loading dose 2 mg/kg then 0.5-1 mg/kg q6h for 5 d | Acute exacerbation of COPD; severe, persistent asthma, PCP<br>Status asthmaticus | Endocrine (hirsutism, DM/glucose intolerance, Cushing's syndrome, HPA axis suppression), GI (increased appetite, indigestion), ocular (cataracts, glaucoma), edema, AVN, osteoporosis, H/A, psychiatric (anxiety, insomnia), easy bruising |
| **ADJUNCT AGENTS** | | | | |
| | theophylline (Uniphyll®) | 400-600 mg OD | Treatment of symptoms of reversible airway obstruction due to COPD | GI upset, diarrhea, N/V, anxiety, H/A, insomnia, muscle cramp, tremor, tachycardia, PVCs, arrhythmias<br>Toxicity: persistent, repetitive vomiting, seizures |
| **LEUKOTRIENE ANTAGONISTS** | | | | |
| | montelukast (Singular®)<br>zafirlukast (Accolate®) | 10 mg PO qhs, now only available as once daily slow release 20 mg bid | Prophylaxis and chronic treatment of asthma | H/A, dizziness, fatigue, fever, rash, dyspepsia, cough, flu-like symptoms |
| **ANTI-IgE MONOCLONAL ANTIBODIES** | | | | |
| | omalizumab (Xolair®) | 150-375 mg SC q2-4wk | Moderate-severe persistant asthma | H/A, sinusitis, pharyngitis, URTI, viral infection, thrombocytopenia, anaphylaxis |
| **PDE-4 INHIBITORS** | | | | |
| | roflumilast (Daxas®) | 500 µg PO OD | Severe emphysema, with frequent exacerbations | Weight loss, suicidal ideation |
| **ANTIBIOTICS – COMMUNITY ACQUIRED PNEUMONIA** | | | | |
| **Macrolide** | erythromycin<br>azithromycin<br>clarithromycin | 250-500 mg PO tid x 7-10 d<br>500 mg PO x 1 dose, then 250 mg OD x 4<br>1000 mg od or 500 mg PO bid x 7-10 d | Alternate to doxycycline or fluoroquinolone | GI (abdominal pain, diarrhea, N/V), H/A, prolonged QT, ventricular arrhythmias, hepatic impairment<br>GI (diarrhea, N/V, abdominal pain), renal failure, deafness<br>H/A, rash, GI (diarrhea, N/V, abnormal taste, heartburn, abdominal pain), increased urea |
| **Doxycycline** | | 100 mg PO bid x 7-10 d | Alternate to macrolide or fluoroquinolone | Photosensitivity, rash, urticaria, anaphylaxis, diarrhea, entercolitis, tooth discolouration in children |
| **Fluoroquinolone** | levofloxacin (Levaquin®)<br>moxifloxacin (Avelox®) | 500 mg PO OD x 7-10 d<br>400 mg PO OD x 7 d | Alternate to macrolide or doxycycline | CNS (dizziness, fever, H/A), GI (N/V, diarrhea, constipation), prolonged QT |
| **ANTIBIOTICS – HOSPITAL ACQUIRED PNEUMONIA** | | | | |
| **3rd gen Cephalosporin** | ceftriaxone (Rocephin®) | 1-2 g IV OD x 7-10 d | Combine with fluoroquinolone or macrolide | Rash, diarrhea, eosinophilia, thrombocytosis, leukopenia, elevated transaminases |
| **Fluoroquinolone** | levofloxacin<br>moxifloxacin | 750 mg PO OD x 5 d<br>400 mg PO OD x 7 d (5 d for AECOPD) | Combine with 3rd gen cephalosporin | Rash, diarrhea, eosinophilia, thrombocytosis, leukopenia, elevated transaminases |
| **Piperacillin/Tazobactam (Tazocin®)** | | 4.5 g IV q6-8h x 7-10 d | Suspect Pseudomonas | CNS (confusion, convulsions, drowsiness), rash<br>Hematologic (abnormal platelet aggregation, prolonged PT, positive Coombs) |
| **Vancomycin (Vancocin®)** | | 1 g IV bid x 7-10 d | Suspect MRSA | CNS (chills, drug fever), hematologic (eosinophilia), rash, red man syndrome, interstitial nephritis, renal failure, ototoxicity |
| **Macrolide** | azithromycin<br>clarithromycin | 500 mg IV OD x 2 d, then 500 mg PO OD x 5 d<br>1000 mg od or 500 mg PO bid x 7-10 d | Suspect Legionella | CNS (chills, drug fever), hematologic (eosinophilia), rash, red man syndrome, interstitial nephritis, renal failure, ototoxicity |

**Table 32. Common Medications for Respiratory Diseases** (continued)

| | Drug | Typical Adult Dose | Indications | Side Effects |
|---|---|---|---|---|
| **ICU MEDICATIONS** | | | | |
| **Pressors/Inotropes** | norepinephrine (Levophed®)<br>phenylephrine<br>dobutamine | 0.5-30 µg/min IV<br>0.5 µg/kg/min IV<br>2-20 µg/kg/min IV | Acute hypotension<br>Severe hypotension<br>Inotropic support | Angina, bradycardia, dyspnea, hyper/hypotension, arrhythmias<br>See above |
| **Sedatives/Analgesia** | fentanyl (opioid class)<br><br>propofol (anesthetic) | 50-100 µg then 50-unlimited µg/h IV<br>1-3 mg/kg then 0.3-5 mg/kg/h IV | Sedation and/or analgesia<br>Sedation and/or analgesia | Bradycardia, respiratory depression, drowsiness, hypotension<br>Apnea, bradycardia, hypotension (good for ventilator sedation) |

See Infectious Diseases, ID24 – for the management of pulmonary tuberculosis

# Landmark Respirology Trials

| Trial | Reference | Results |
|---|---|---|
| ARDS Network | NEJM 2000;342:1301-8 | Mortality decreased in ARDS patients ventilated with a low tidal volume strategy |
| Berlin Criteria | JAMA 2012;307:2526-33 | The new definition of ARDS, better predicts mortality |
| CPAP and Apnea | NEJM 2005;353:2025-33 | CPAP ameliorates symptoms of sleep apnea but does not affect mortality in CHF |
| EINSTEIN-PE | NEJM 2012;366:1287-97 | Fixed dose of rivoxabarin was non-inferior to standard therapy (Vit K antagonist) initial and long-term treatment of PE |
| Emphysema Treatment Trial | NEJM 2003;348:2059-73 | Lung volume reduction surgery benefits patients with upper lobe disease and low exercise capacity |
| IELCAP | NEJM 2006;355:1763-71 | High survival rate in patients with early stage lung cancer detected by low dose CT screening |
| Lung Health | JAMA 1994;272:1497-505 | Aggressive smoking intervention significantly decreases the age-related decline in $FEV_1$ in middle-aged smokers with mild airways obstruction |
| OSCILLATE | NEJM 2013;368: 795-805 | Early high-frequency oscillatory ventilation in patients with moderate to severe ARDS might increase in-hospital mortality |
| ILD | NEJM 1978;298:801-9 | Interstitial lung disease subsets have different prognoses and response to treatment (e.g. desquamative but not usual interstitial pneumonia respond well to corticosteroids) |
| POET-COPD | NEJM 2011;364:1093-103 | Tiotropium decreases the number of moderate-to-severe exacerbations in comparison to salmeterol |
| REDUCE | JAMA 2013;309: 2223-2231 | 5 d course of glucocorticoids is non-inferior to a 14 d course for treatment of acute COPD exacerbations |
| ROFLUMILAST | Lancet 2009;374:695-703 | Phosphodiesterase-4 inhibitor improves $FEV_1$ when used as add-on therapy in COPD patients on tiotropium or salmeterol |
| TORCH | NEJM 2007;356:775-89 | Combination of inhaled steroids and long-acting β2-agonists improves COPD symptoms, reduces exacerbations, and shows a trend to lowers mortality |
| UPLIFT | NEJM 2008;359:1543-54 | Tiotropium improves symptoms of COPD with fewer exacerbations, but does not affect $FEV_1$ decline |

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Notes

# RH Rheumatology

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# Acronyms

| | |
|---|---|
| Ab | antibody |
| ACPA | anti-citrullinated protein antibodies |
| Ag | antigen |
| ANA | antinuclear antibody |
| ANCA | antineutrophil cytoplasmic antibody |
| Anti-RNP | antiribonuclear protein |
| Anti-Sm | anti-Smith antibodies |
| Anti-SRP | anti-signal recognition particle |
| Anti-SSA | anti-Sjögren's syndrome antigen A |
| APLA | antiphospholipid antibodies |
| APLS | antiphospholipid antibody syndrome |
| aPTT | activated partial thromboplastin time |
| AS | ankylosing spondylitis |
| AVN | avascular necrosis |
| BlyS | B-lymphocyte stimulator |
| BUN | blood urea nitrogen |
| CBC | complete blood count |
| CCB | calcium channel blocker |
| CCP | cyclic citrullinated peptide |
| CK | creatine kinase |
| CMC | carpometacarpal joint |
| CNS | central nervous system |
| CTD | connective tissue disease |
| CPPD | calcium pyrophosphate dihydrate |
| CRP | C-reactive protein |
| CVA | cerebrovascular accident |
| CVS | cardiovascular system |
| DAT | direct antiglobulin test |
| DEXA | dual energy X-ray absorptiometry |
| DIP | distal interphalangeal joint |
| DM | diabetes mellitus |
| DMARD | disease-modifying anti-rheumatic drug |
| DMM | dermatomyositis |
| dsDNA | double stranded DNA |
| EA | enteropathic arthritis |
| ECASA | enteric-coated acetylsalicylic acid |
| ESR | erythrocyte sedimentation rate |
| FVC | forced vital capacity |
| GC | Neisseria gonorrhoeae gonococcus |
| GCA | giant cell arteritis |
| GPA | granulomatosis with polyangiitis |
| H/A | headache |
| Hb | hemoglobin |
| HLA | human leukocyte antigen |
| IA | intra-articular |
| IBD | inflammatory bowel disease |
| IE | infective endocarditis |
| ILD | interstitial lung disease |
| IP | interphalangeal joint |
| ITP | idiopathic thrombocytopenic purpura |
| LDH | lactate dehydrogenase |
| MCP | metacarpalphalangeal joint |
| MCTD | mixed connective tissue disease |
| MHC | major histocompatibility complex |
| MPO | myeloperoxidase |
| MTP | metatarsal phalangeal joint |
| MTX | methotrexate |
| OA | osteoarthritis |
| PAN | polyarteritis nodosa |
| PIP | proximal interphalangeal joint |
| PM | polymyositis |
| PMN | polymorphonuclear leukocyte |
| PMR | polymyalgia rheumatica |
| PR3 | proteinase 3 |
| PsA | psoriatic arthritis |
| PTT | partial thromboplastin time |
| PUD | peptic ulcer disease |
| RA | rheumatoid arthritis |
| RBC | red blood cell |
| ReA | reactive arthritis |
| RF | rheumatoid factor |
| ROM | range of motion |
| SI | sacroiliac |
| SLE | systemic lupus erythematosus |
| SNRI | serotonin-norepinephrine reuptake inhibitors |
| SS | Sjögren's syndrome |
| SSA | Sjögren's syndrome antigen A |
| SSB | Sjögren's syndrome antigen B |
| SSc | systemic sclerosis |
| TNF | tumour necrosis factor |
| TTP | thrombotic thrombocytopenic purpura |
| U/A | urinalysis |
| ULN | upper limit of normal |
| U-SpA | undifferentiated spondyloarthropathy |
| VDRL | venereal disease research laboratory |
| WBC | white blood cell |

# Anatomy of Joint Pathology

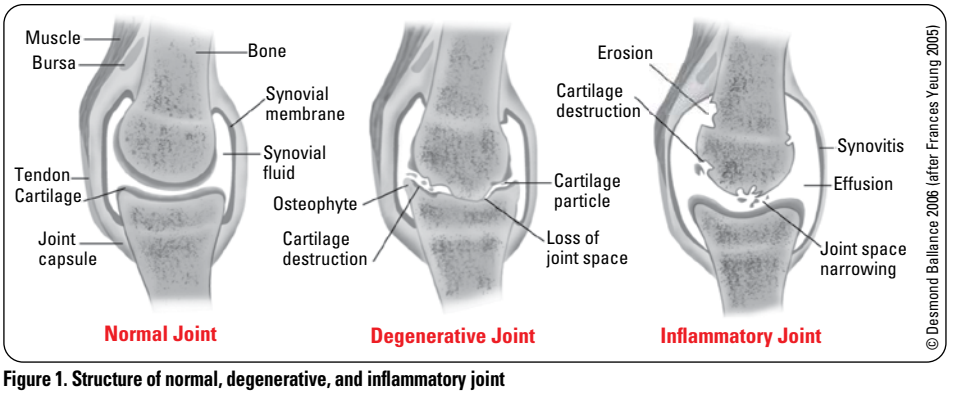



**Figure 1. Structure of normal, degenerative, and inflammatory joint**

**Terminology in Rheumatology**

**Arthritis**
- Joint swelling: effusion/synovial thickening
- Decreased ROM
- Stress pain (pain at the end of ROM)
- Increased warmth

**Arthralgia**: perception of joint pain without obvious clinical findings
**Active Joint**: swollen joint, joint line tenderness, or stress pain

**Innate Immune Cells**
- **Neutrophil (PMN):** circulate in blood and respond to inflammatory stimuli, kill invading organisms by phagocytosis, degranulation, and neutrophil extracellular traps
- **Natural Killer Cell:** innate immunity against intracellular infections (especially viruses), killing function, and produce cytokines
- **Macrophage:** arrive after PMNs, suppress PMN efflux and phagocytose PMN debris, secrete pro-inflammatory cytokines in response to microbial debris
- **Dendritic Cell:** actively phagocytic when immature, activated by signals from toll-like receptor (TLR), release pro-inflammatory cytokines, present antigens to T cells in lymph nodes
- **Eosinophil:** respond to inflammatory cytokines and degranulate, releasing reactive oxygen species, and cytokines, associated with allergy, asthma, and parasitic infection
- **Mast Cell:** present in connective tissue and mucosa, allergen cross-linking of IgE bound to mast cell triggers degranulation and release of inflammatory mediators

# Basics of Immunology

## Immune Mechanisms of Disease

**Table 1. Mechanisms of Immune-Mediated Disorders**

| Type | Pathophysiology | Examples |
|---|---|---|
| **Immediate Hypersensitivity (Type I)** | Formation of IgE → release of immunologic mediators from basophils/mast cells → diffuse inflammation | Asthma, allergic rhinitis, anaphylaxis |
| **Cytotoxic (Type II)** | Formation of Ab → deposit and bind to Ag on cell surface → phagocytosis or lysis of target cell | Autoimmune hemolytic anemia, anti-glomerular basement membrane disease (Goodpasture syndrome), Graves' disease, pemphigus vulgaris, rheumatic fever, ITP |
| **Immune Complex (Type III)** | Formation and deposition of Ag-Ab complexes → activate complement → leukocyte recruitment and activation → tissue injury | SLE, PAN, post-streptococcal glomerulonephritis, serum sickness, viral hepatitis |
| **Cell-Mediated/Delayed Hypersensitivity (Type IV)** | Release of cytokines by sensitized T cells and T cell mediated cytotoxicity | Contact dermatitis, insect venom, mycobacterial proteins |

## Immunogenetics and Disease

- cell surface molecules called HLAs play a role in mediating immune reactions
- MHC are genes on the short arm of chromosome 6 that encode HLA molecules
- certain HLA haplotypes are associated with increased susceptibility to autoimmune diseases

**Table 2. Classes of MHCs**

| MHC Class | Types | Location | Function |
|---|---|---|---|
| **I** | HLA-A, B, C | All cells | Recognized by CD8+ (cytotoxic) T-lymphocytes |
| **II** | HLA-DP, DQ, DR | Ag presenting cells (mononuclear phagocytes, B cells, etc.) | Recognized by CD4+ (helper) T-lymphocytes |
| **III** | Some components of the complement cascade | In plasma | Chemotaxis, opsonization, lysis of bacteria and cells |

**Table 3. HLA-Associated Rheumatic Disease**

| HLA Type | Associated Conditions | Comments |
|---|---|---|
| **B27** | Ankylosing Spondylitis (AS)<br>Reactive Arthritis (ReA)<br>Enteropathic Arthritis (EA) (axial)<br>Psoriatic Arthritis (PsA) (axial) | Relative risk 20x for developing AS and ReA |
| **DR4, DR1** | Rheumatoid Arthritis (RA) | In RA, relative risk = 2-10x; found in 93% of patients |
| **DR3** | Sjögren's syndrome (SS)<br>Systemic Lupus Erythematosus (SLE) | DR3 is associated with the production of anti-Ro/SSA and anti-La/SSB antibodies |

# Differential Diagnoses of Common Presentations

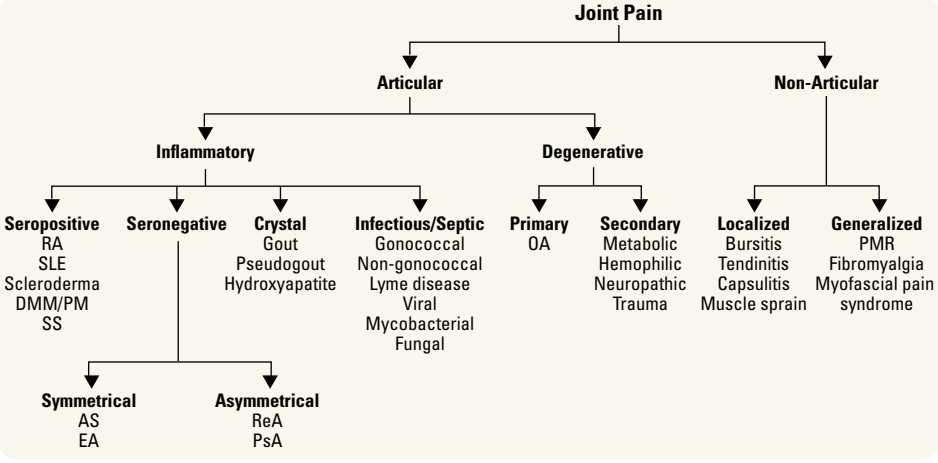



**Figure 2. Clinical approach to joint pain**

**Table 4. Differential Diagnosis of Monoarthritis**

| ACUTE MONOARTHRITIS | | | | |
|---|---|---|---|---|
| **Non-Inflammatory** | **Inflammatory** | | **Infectious** | **Hemorrhagic** |
| **Trauma** | **Crystal induced**<br>Monosodium urate (MSU-gout)<br>Calcium pyrophosphate dehydrate (CPPD) or pseudogout<br>Hydroxyapatite (HA) | **Non-crystal induced**<br>Seropositive<br>Seronegative | Most bacterial infections, e.g.: *S. aureus, GC*<br>viral arthopathies are rarely monoarticular | Trauma, fracture, blood dyscrasias, and anticoagulants<br>Congenital clotting disorders e.g. hemophilia |

| CHRONIC MONOARTHRITIS | | | |
|---|---|---|---|
| **Non-Inflammatory** | **Inflammatory** | **Infectious** | **Hemorrhagic** |
| OA and osteonecrosis | Serpositive<br>Seronegative | TB and fungi | Tumour |

**Table 5. Differential Diagnosis of Oligoarthritis/Polyarthritis**

| ACUTE (<6 wk) | CHRONIC (>6 wk) | | |
|---|---|---|---|
| Post-viral infection (parvovirus B19, HIV)<br>Post-bacterial infection (GC and non-GC, rheumatic fever)<br>Crystal induced<br>Other (sarcoidosis, Lyme disease)<br>Very early rheumatoid arthritis (VERA) | **Seropositive inflammatory arthritis**<br>RA<br>SLE<br>Scleroderma<br>DMM/PM | **Seronegative inflammatory arthritis**<br>AS<br>EA<br>PsA<br>ReA<br>Crystal (polyarticular gout) | **Degenerative**<br>OA |

**Key Cytokine Targets of Biologic Drugs**

**TNF**
- **Source of cytokine**: T cells, macrophages
- **Major Functions**: cachexia, induces other cytokines, T cell stimulation, induces metalloproteinases and prostaglandins, increases expression of adhesion molecules; increases vascular permeability leading to increased entry of IgG, complement and cells into tissues

**IL-6**
- **Source of cytokine**: Many cells including monocytes and macrophages
- **Major Functions**: anemia of inflammation (hepcidin production), proliferation of B and T cells, acute phase reactant, induces natural protease inhibitor, promotes erosions, induces elevated CRP

**Adaptive Immune Cells**
- **B-cell**: produce antibodies after activation by specific antigen and B-cell co-receptor, additional signals provided by CD4 T helper cells
- **Cytotoxic T cell**: CD8, direct cytotoxicity of target cells at sites of infection, kill via lytic granules and FasL-Fas interaction, recognize specific antigen and MHC1
- **Helper T cell**: subset of CD4 cells, activate and help other types of cells carry out immune defense (activate macrophages, help B cells, release cytokines)
- **Regulatory T cell**: subset of CD4 cells, suppress activation of naïve autoreactive T cells

**Causes of Joint Pain**

**SOFTER TISSUE**
**S**epsis
**O**A
**F**racture
**T**endon/muscle
**E**piphyseal
**R**eferred
**T**umour
**I**schemia
**S**eropositive arthritides
**S**eronegative arthritides
**U**rate (gout)/other crystal
**E**xtra-articular rheumatism (PMR/fibromyalgia)

**Patterns of Joint Involvement**
- Symmetrical vs. asymmetrical
- Small vs. large
- Mono vs. oligo (2-4 joints) vs. polyarticular (≥5 joints)
- Axial vs. peripheral

**Table 6. Symptoms of Inflammatory Arthritis vs. Degenerative Arthritis**

| Inflammatory | Degenerative |
|---|---|
| Pain at rest, relieved by gentle motion | Pain with motion, relieved by rest |
| Morning stiffness >1 h | Morning stiffness <1/2 h |
| Warmth, swelling, erythema | Joint instability, buckling, locking |
| Malalignment/deformity (late finding) | Bony enlargement, malalignment/deformity (late finding) |
| Extra-articular manifestations | Evening/end of day pain |
| Nighttime awakening due to pain | |



The presence of synovitis often indicates articular as opposed to non-articular joint pain; synovitis presents with: soft tissue swelling, effusion, warmth, and pain with movement

**Table 7. Seropositive vs. Seronegative Rheumatic Diseases**

| | Seropositive | Seronegative |
|---|---|---|
| **Demographics** | F>M | M>F |
| **Peripheral Arthritis** | Symmetrical<br>Small (PIP, MCP) and medium joints (wrist, knee, ankle, elbow) common<br>DIP less often involved | Usually asymmetrical<br>Usually larger joints, lower extremities (exception: PsA)<br>DIP in PsA<br>Dactylitis ("sausage digit") |
| **Pelvic/Axial Disease** | No (except for C-spine) | Yes |
| **Enthesitis** | No | Yes |
| **Extra-Articular** | Nodules<br>Vasculitis<br>Sicca<br>Raynaud's phenomenon<br>Rashes, internal organ involvement (lung, cardiac)<br>Entrapment neuropathies (i.e. carpal tunnel syndrome) | Iritis (anterior uveitis)<br>Oral ulcers<br>Gastrointestinal<br>Dermatological (psoriasis or keratodermia)<br>Genitourinary inflammation |



**Monitoring CRP**
**Advantages**
- Unaffected by age/gender
- Rapid response to inflammatory stimulus
- Wide range of clinically relevant values
- Can be measured on stored sera
- Quantification precise/reproducible

**Disadvantages**
- More expensive

# Synovial Fluid Analysis

- synovial fluid is an ultrafiltrate of plasma plus hyaluronic acid; it lubricates joint surfaces and nourishes articular cartilage

## Indications
- diagnostic: to clarify cause of an acute monoarthritis; to analyze fluid for cell count to differentiate inflammatory or degenerative; can be diagnostic for septic vs. crystal-induced vs. hemarthrosis in unexplained joint, bursa or tendon sheath swelling
- therapeutic: drainage of blood, purulent or tense effusions; corticosteroid injection in absence of sepsis

## Contraindications to Joint Aspiration or Injection
- absolute: open lesion or suspected infection of overlying skin or soft tissue
- relative: bleeding diathesis, thrombocytopenia, prosthetic joint

## Synovial Fluid Analysis
- most important to assess the 3C's: cell count (WBC), differential culture and Gram stain, and crystal analysis
- other parameters to consider are listed in Table 8



**Most Important Tests of Synovial Fluid (3 Cs)**
1. **C**ulture and Gram stain
2. **C**ell count and differential
3. **C**rystal examination (protein, LDH, glucose less helpful)

**Table 8. Synovial Fluid Analysis**

| Parameter | Normal | Non-Inflammatory | Inflammatory | Infectious | Hemorrhagic |
|---|---|---|---|---|---|
| **Colour** | Pale yellow | Pale yellow | Pale yellow | Yellow to white | Red/brown |
| **Clarity** | Clear | Clear | Opaque | Opaque | Sanguinous |
| **Viscosity** | High | High | Low | Low or paradoxically high if purulent | Variable |
| **WBC/mm$^3$** | <200 | <2000 | ≥2000 (crystal induced arthritis – often much higher than 2000) | >2000 (>50,000) | Variable |
| **% PMN** | <25% | <25% | ≥25% | >75% | Variable |
| **Culture/Gram Stain** | – | – | – | Usually positive | – |
| **Examples** | | Trauma<br>OA<br>Neuropathy<br>Hypertrophic – arthropathy | Seropositive<br>Seronegative<br>Crystal arthropathies | *S. aureus*<br>Gram negative<br>GC → difficult to culture, (may have a low WBC) | Trauma<br>Hemophilia |



**Choosing Wisely Canada Recommendations**
1. Do not order ANA as a screening test in patients without specific signs or symptoms of SLE or another CTD
2. Do not order an HLA-B27 unless spondyloarthritis is suspected based on specific signs or symptoms
3. Do not repeat DEXA scans more often than every 2 yr
4. Do not prescribe bisphosphonates for patients at low risk of fracture
5. Do not perform whole body bone scans (e.g. scintigraphy) for diagnostic screening for peripheral and axial arthritis in the adult population

# Septic Arthritis

- septic arthritis is a medical emergency, it can lead to rapid joint destruction and has a 10-15% risk of mortality
- knee and hip are most commonly affected joints, with knee accounting for approximately 50% of cases
- most commonly caused by hematogenous spread of bacterial infection (gram positive cocci > Gram negative bacilli)
- risk factors: very young or very old age (>80), portal of entry (IV drug use), recent infection, RA (related to prior joint damage and immunosuppressed state of host), type 2 DM
- poor prognostic factors: older age, immunocompromised, delay in treatment, previously damaged joint, joint prosthesis
- consider empiric antibiotic therapy until septic arthritis is excluded from history, physical examination, and synovial fluid analysis and culture
- see Infectious Diseases, ID11 and Orthopedic Surgery, *Septic Joint* OR11

Septic arthritis is a medical emergency; it leads to rapid joint destruction, and there is a 10-15% risk of mortality

# Degenerative Arthritis: Osteoarthritis

- see Family Medicine, FM40

## Definition

- progressive deterioration of articular cartilage and surrounding joint structures caused by genetic, metabolic, biochemical, and biomechanical factors with secondary components of inflammation

## Classification (Based on Etiology)

- primary (idiopathic)
  - most common, unknown etiology
- secondary
  - post-traumatic or mechanical
  - post-inflammatory (e.g. RA) or post-infectious
  - heritable skeletal disorders (e.g. scoliosis)
  - endocrine disorders (e.g. acromegaly, hyperparathyroidism, hypothyroidism)
  - metabolic disorders (e.g. gout, pseudogout, hemochromatosis, Wilson's disease, ochronosis)
  - neuropathic (e.g. Charcot joints)
    - atypical joint trauma due to peripheral neuropathy (e.g. DM, syphilis)
  - avascular necrosis (AVN)
  - other (e.g. congenital malformation)

## Pathophysiology

- the process appears to be initiated by abnormalities in biomechanical forces and/or, less often, in cartilage
- elevated production of pro-inflammatory cytokines is important in OA progression
- tissue catabolism > repair
- contributing factors (mechanisms unknown): genetics, alignment (bow-legged, knock-kneed), joint deformity (hip dysplasia), joint injury (meniscal or ligament tears), obesity, environmental, mechanical loading, age, and gender
- now considered to be a systemic musculoskeletal disorder rather than a focal disorder of synovial joints

## Epidemiology

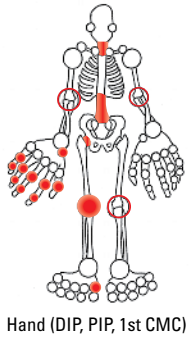
- most common arthropathy (accounts for ~75% of all arthritis)
- increased prevalence with increasing age (35% of 30 yr olds, 85% of 80 yr olds)

## Risk Factors

- genetic predisposition, advanced age, obesity (for knee and hand OA), female, trauma

OA of MCP joints can be seen in hemochromatosis or CPPD-related disease (chondrocalcinosis)

**ESR** can also be elevated in anemia, end-stage renal disease, females, increased age, and obesity



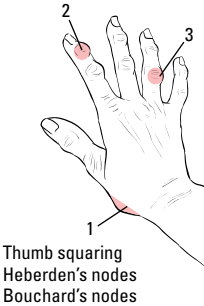
- Hand (DIP, PIP, 1st CMC)
- Hip
- Knee
- 1st MTP
- L-spine (L4-L5, L5-S1)
- C-spine
- Uncommon: ankle, shoulder, elbow, MCP, rest of wrist

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**Figure 3. Common sites of joint involvement in OA**

**Table 9. Signs and Symptoms of OA**

| Signs | Symptoms |
|---|---|
| Joint line tenderness; stress pain ± joint effusion | Joint pain with motion; relieved with rest |
| Bony enlargement at affected joints | Short duration of stiffness (<1/2 h) after immobility, called gelling |
| Malalignment/deformity (angulation) | Joint instability/buckling (often due to ligamentous instability) |
| Limited ROM | Joint locking due to "joint mouse" (bone or cartilage fragment) |
| Crepitus on passive ROM | Loss of function (e.g. meniscal tear or other internal derangements) |
| Inflammation (mild if present) | Insidious onset of pain, localized to affected joints |
| Periarticular muscle atrophy | Fatigue, poor sleep, impact on mood |




1. Thumb squaring
2. Heberden's nodes
3. Bouchard's nodes

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**Figure 4. Hand findings in OA**

### Joint Involvement

- generalized osteoarthritis: 3+ joint groups
- asymmetric (knees usually affected bilaterally)
- hand
  - DIP (Heberden's nodes = osteophytes → enlargement of joints)
  - PIP (Bouchard's nodes)
  - CMC (usually thumb squaring)
  - 1st MCP (other MCPs are usually spared)
- hip
  - usually presents as groin pain ± dull or sharp pain in the trochanteric area, internal rotation and abduction are lost first
  - pain can radiate to the anterior thigh, but generally does not go below the knee
- knee
  - initial narrowing of one compartment, medial > lateral; seen on standing x-rays, often patellar-femoral joint involved
- foot
  - common in first MTP and midfoot
- lumbar spine
  - very common, especially L4-L5, L5-S1
  - degeneration of intervertebral discs and facet joints
  - reactive bone growth can contribute to neurological impingement (e.g. sciatica, neurogenic claudication) or spondylolisthesis (forward or backward movement of one vertebra over another)
- cervical spine
  - commonly presents with neck pain that radiates to scapula, especially in mid-lower cervical area (C5 and C6)

**Differential Diagnosis of Elevated ESR**
- Systemic inflammatory diseases
- Localized inflammatory diseases
- Malignancy
- Trauma
- Infection
- Tissue injury/ischemia

### Investigations

- blood work
  - normal CBC and ESR, CRP
  - negative RF and ANA
- radiology: 4 hallmark findings, see sidebar
- synovial fluid: non-inflammatory (see Table 8)

**The Radiographic Hallmarks of OA**
- Joint space narrowing
- Subchondral sclerosis
- Subchondral cysts
- Osteophytes

### Treatment

- presently no treatment alters the natural history of OA
- prevention: prevent injury, weight management, maintenance of muscle strength
- **non-pharmacological therapy**
  - weight loss (minimum 5-10 lb loss) if overweight
  - physiotherapy: heat/cold, low impact exercise programs
  - occupational therapy: aids, splints, cane, walker, bracing
- **pharmacological therapy** (see Table 34, RH29)
  - 1st line with few joints affected, knee, hand – topical: transdermal NSAIDs preparations, capsaicin
  - 1st line with multiple joints, hip – oral: acetaminophen/NSAIDs
  - treat neuropathic pain if present (anti-depressants, anti-epileptics, etc.)
  - joint injections: corticosteroid (sparse use, effective for short-term treatment), hyaluronic acid (little evidence of benefits)
  - glucosamine ± chondroitin (efficacy not supported)
- **surgical treatment**
  - total and/or partial joint replacement, joint debridement (not shown to be effective), osteotomy, fusion

# Seropositive Rheumatic Disease

- diagnosis vs. classification in rheumatology
  - diagnostic criteria are selected for sensitivity, as opposed to specificity, thus may misdiagnose some cases
  - classification criteria are developed for specificity so well-defined cases can be studied in clinical trials
  - modern classification criteria are more sensitive and specific for diagnostic use in studies of earlier disease
- seropositive arthropathies are characterized by the presence of a serologic marker such as positive RF or ANA
- a small subset of the vasculitides, the small vessel ANCA-associated vasculitides, have a measurable serological component, but they are often considered a separate entity from seropositive disease by experts

**Table 10. Autoantibodies and their Prevalence in Rheumatic Diseases**

| Autoantibody | Disease | Healthy Controls | Comments |
|---|---|---|---|
| **RF** | RA 80%<br>SS 50%<br>SLE 20% | <5%<br>10-20%<br>>65 | Serologic hallmark of RA<br>Autoantibodies directed against Fc domain of IgG<br>Sensitive in RA (can be negative early in disease course), levels correlate with disease activity<br>May be present in ANA positive diseases, often in lower titre<br>Non-specific; may be present in IE, TB, hepatitis C, silicosis, sarcoidosis |
| **Anti-CCP** | RA 80% | | Specific for RA (94-98%)<br>May be useful in early disease and to predict aggressive disease, can occur before clinical disease apparent |
| **ANA** | SLE 98%<br>MCTD 100%<br>SS 40-70%<br>CREST 60-80%<br>(Often seen in other CTDs) | High titers <5%<br>Low titers<br>Up to 30%,<br>Prevalence of non-disease related ANA rises with age | Ab against nuclear components (DNA, RNA, histones, centromere)<br>Sensitive but not specific for SLE<br>Given high false positive rate - only measure when high pre-test probability of CTD |
| **Anti-dsDNA** | SLE 50-70% | 0% | Specific for SLE (95%)<br>Levels correlate with disease activity (i.e. SLE flare) |
| **Anti-Sm** | SLE <30% | 0% | Specific but not sensitive for SLE<br>Does not correlate with SLE disease activity<br>If positive, will remain positive through disease course |
| **Anti-Ro (SSA)** | SS 40-95%<br>SSc 21%<br>SLE 32%<br>RA 15% | 0.5% | Subacute cutaneous SLE (74%)<br>May be only Ab present in ANA negative SLE<br>Increases risk of having child with neonatal lupus syndrome |
| **Anti-La (SSB)** | SS 40%<br>SLE 10% | 0% | Usually occurs with anti-Ro<br>Specific for SS and SLE when anti-Ro is also positive<br>Increases risk of having child with neonatal lupus syndrome |
| **Antiphospholipid Ab (LAC, aCLA, a$B_2$GP)** | APLS 100%<br>SLE 31-40% | <5% | By definition, present in APLS<br>Only small subset of SLE patients develop clinical syndrome of APLS<br>If positive, will often get a false positive VDRL test |
| **Anti-Histone** | Drug-induced SLE 95%<br>SLE 30-80% | 0%<br>0% | Highly specific for drug-induced SLE |
| **Anti-RNP** | MCTD<br>SLE | | High titres present in MCTD; present in many other CTDs (especially SLE) |
| **Anti-Centromere** | Limited SSc (CREST) >80% | 0% | Specific for CREST, limited cutaneous variant of systemic sclerosis |
| **Anti-Topoisomerase I (formerly Scl-70)** | Diffuse SSc 26-76% | 0% | Specific for SSc<br>Increased risk pulmonary fibrosis in SSc |
| **Anti-Jo1** | PM DMM | 0% | Less frequent for DMM |
| **c-ANCA** | Active GPA >90% | 0% | Specific and sensitive |
| **p-ANCA** | GPA 10%<br>Other vasculitis | 0% | Nonspecific and poor sensitivity (found in ulcerative colitis, PAN, microscopic polyangiitis, Churg-Strauss, rapidly progressive glomerulonephritis) |
| **Anti-Mi-2** | DMM 15-20% | | Specific but not sensitive (not available in all centres) |
| **Ab Against RBCs, WBCs, or Platelets** | SLE | | Perform direct antiglobulin test (DAT), test Hb, reticulocyte, leukocyte, and platelet count, antiplatelet Abs |
| **Anti-mitochondria** | Primary biliary cholangitis | 0% | Sensitive and specific |

Note: some individuals in the normal population test positive for RF and/or ANA, but do not have the conditions listed above

# Connective Tissue Disorders

**Table 11. Features of Seropositive Arthropathies**

| | RA | SLE | Scleroderma | Dermatomyositis |
|---|---|---|---|---|
| **CLINICAL FEATURES** | | | | |
| **History** | Symmetrical polyarthritis (small joint involvement)<br>Morning stiffness (>1 h) | Multisystemic disease: rash, photosensitivity, Raynaud's, alopecia, cardiac and pulmonary serositis, CNS symptoms, glomerulonephritis | Skin tightness, stiffness of fingers, Raynaud's, heartburn, dysphagia, shortness of breath on exertion due to pulmonary HTN or ILD, renal crisis with new onset HTN or hypertensive urgency/emergency, dyspnea on exertion | Heliotrope rash (periorbital), Gottron's papules (violaceous papules over knuckles and IP joints) ± poikiloderma<br>Shawl sign: macular erythema over chest and shoulder<br>Proximal muscle weakness > pain, dyspnea on exertion |
| **Physical Examination** | Early: Effused joints<br>Tenosynovitis<br>Subcutaneous nodules<br>Other extra-articular manifestations<br>Late: Joint deformities<br>Bone-on-bone crepitus in advanced disease | Confirm historical findings (rash, serositis, renal, CVS, etc.)<br>± effused (typically small) joints (can be minimal, look for soft tissue swelling) | Skin tightness on dorsum of hand, facial skin tightening, telangiectasia, calcinosis, non-effused joint, inspiratory crackles, features of right side heart failure | Rash, proximal muscle weakness, inspiratory crackles |
| **LABORATORY** | | | | |
| **Non-Specific** | ↑ ESR in 50-60%<br>↑ CRP<br>↑ Platelets<br>↓ Hb (chronic disease)<br>↓ WBC (neutropenia rare) | ↑ ESR<br>↓ Platelets (autoimmune)<br>↓ Hb (autoimmune)<br>↓ WBC (leukopenia, lymphopenia) | ↑ ESR<br>↓ Hb<br>Normal WBC | Possible increased ESR<br>↑ CRP<br>↓ Hb<br>Normal WBC |
| **Specific** | RF +ve in ~80%<br>Anti-CCP +ve in ~80% | ANA +ve in 98%<br>Anti-dsDNA +ve in 50-70%<br>Anti-SM +ve in 30%<br>↓ C3, C4, total hemolytic complement<br>False positive VDRL (in SLE subtypes)<br>↑ PTT (in SLE subtypes, e.g. APLA) | ANA +ve in >90%<br>Anti-topoisomerase 1 (diffuse)<br>Anti-centromere (usually in *CREST*, see sidebar RH13) | CK elevated in 80%<br>ANA +ve in 33%<br>Anti-Jo-1, anti-Mi-2<br>Muscle biopsy<br>EMG<br>MRI |
| **Radiographs** | Very Early: normal<br>Early: Periarticular osteopenia<br>Later: Joint space narrowing<br>Erosions<br>Symmetric/concentric | Non-erosive<br>± Osteopenia<br>± Soft tissue swelling | ± Pulmonary fibrosis<br>± Esophageal dysmotility<br>± Calcinosis<br>± ILD | ± Esophageal dysmotility<br>± ILD<br>± Calcifications |

# Rheumatoid Arthritis

## Definition

- chronic, symmetric, erosive synovitis of peripheral joints (e.g. wrists, MCPs, MTPs)
- characterized by inflammatory joint disease ± a number of extra-articular features
- 1 joint with definite clinical synovitis (swelling) not explained by another disease

**Table 12. 2010 ACR/EULAR Classification Criteria for RA (score-based algorithm: add score of categories A-D; a score of 6/10 for definite RA)**

| Criteria | Score | Comments |
|---|---|---|
| A. Joint involvement (swollen or tender) | | |
| 1 large joint (shoulders, elbows, hips, knees, and ankles) | 0 | |
| 2-10 large joints | 1 | |
| 1-3 small joints (MCPs, PIPs, wrists, 2nd-5th MTPs) | 2 | |
| 4-10 small joints | 3 | |
| >10 joints (at least 1 small joint) | 5 | |
| B. Serology | | Total score of ≥6: definite RA<br>Must have ≥1 joint with definite clinical swelling, not better explained by other disease |
| Negative RF and negative Anti-CCP | 0 | |
| Low-positive RF or low-positive Anti-CCP (<3x ULN) | 2 | |
| High-positive RF or high-positive Anti-CCP (>3x ULN) | 3 | |
| C. Acute phase reactants | | |
| Normal CRP and normal ESR | 0 | |
| Abnormal CRP and abnormal ESR | 1 | |
| D. Duration of symptoms | | |
| <6 wk | 0 | |
| ≥6 wk | 1 | |

*Arthritis Rheum* 2010;62:2569-2581

RA is an independent risk factor for atherosclerosis and CV disease. RA is associated with increased overall mortality/morbidity from all causes: CV disease, neoplasm (especially lymphoma), infection

**Common Presentation**

- Morning stiffness >1 h, improves with use
- Symmetric joint involvement
- Initially involves small joints of hands and feet
- Constitutional symptoms

## Pathophysiology

- autoimmune disorder, unknown etiology
- complex interaction of genes and environment leading to breakdown of immune tolerance; many pathways result in autoreactivity leading to a final common pathway to synovial inflammation
  - genetic predisposition: HLA-DR4/DR1 association (93% of patients have either HLA type), cytokine promotors, T cell signaling
    - induction of enzymes that convert arginine to citrulline caused by environmental stress (cigarette smoking)
    - RA: propensity for immune reactivity to neoepitopes created by protein citrullination and production of anti-citrullinated protein antibodies
- once inflammatory process is established, synovium organizes itself into an invasive tissue that degrades cartilage and bone
- progressive bone destruction with absence of bone repair in response to inflammation
  - elevated TNF level increases osteoclasts and decreases osteoblasts at the site of inflammation (results in periarticular osteopenia)
  - upregulation of RANK ligand increases osteoclast-mediated destruction

## Epidemiology

- most common inflammatory arthritis: prevalent in 1% of population
- F:M = 3:1
- age of onset 20-40 yr

## Signs and Symptoms

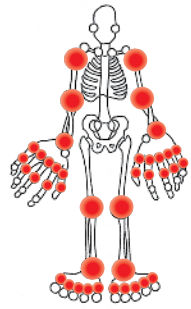
- variable course of exacerbations and remissions
- morning stiffness >1 h, improves with use, worsens with rest
- polyarthritis: symmetric joint involvement (tender, swollen), small joints affected, most commonly in hands and feet (MCP, PIP, MTP)
- constitutional symptoms: profound fatigue, depression, myalgia, weight loss
- extra-articular features
- limitation of function and decrease in global functional status
- complications of chronic synovitis
  - signs of mechanical joint damage: loss of motion, instability, deformity, crepitus, joint deformities
    - swan neck deformity, boutonnière deformity
    - ulnar deviation of MCP, radial deviation of wrist joint
    - hammer toe, mallet toe, claw toe
    - flexion contractures
  - atlanto-axial and subaxial subluxation
    - C-spine instability
      - neurological impingement (long tract signs)
      - difficult/dangerous intubation: risk of worsening subluxation and damage to spinal cord
- limited shoulder mobility, spontaneous tears of the rotator cuff leading to chronic spasm
- tenosynovitis → may cause rupture of tendons
- carpal tunnel syndrome
- ruptured Baker's cyst (outpouching of synovium behind the knee); presentation similar to acute DVT
- poor prognostic factors include: young age of onset, high RF titer, elevated ESR, activity of >20 joints, and presence of extra-articular features

**Table 13. Extra-Articular Features of RA Classified by Underlying Pathophysiology**

| System | Vasculitic | Lymphocytic Infiltrate |
|---|---|---|
| **Skin** | Periungual infarction, cutaneous ulcers, palpable purpura | Rheumatoid nodules (may have vasculitic component) |
| **Ocular** | Episcleritis, scleritis | Keratoconjunctivitis sicca |
| **Head and Neck** | | Xerostomia, Hashimoto's thyroiditis (see Endocrinology, E28) |
| **Cardiac** | | Peri-/myocarditis, valvular disease, conduction defects |
| **Pulmonary** | | Pulmonary fibrosis, pleural effusion, pleuritis, pulmonary nodules |
| **Neurologic** | Peripheral neuropathy: sensory stocking-glove, mononeuritis multiplex | |
| **Hematologic** | | Splenomegaly, neutropenia (Felty's syndrome) |
| **Renal** | | Amyloidosis – caused by accumulation of abnormal proteins |

## Classification of Global Functional Status in RA

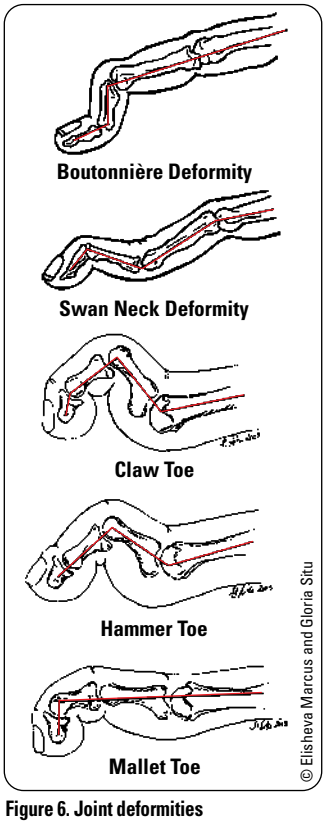
- **Class I**: able to perform usual ADLs (self-care, vocational, avocational)
- **Class II**: able to perform self-care and vocational activities, restriction of avocational activities
- **Class III**: able to perform self-care, restriction of vocational and avocational activities
- **Class IV**: limited ability to perform self-care, vocational, and avocational activities



- PIP
- MCP
- Wrist, not 1st CMC
- Elbow
- Shoulder
- Knee
- Ankle
- MTP
- C-spine

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**Figure 5. Common sites of joint involvement in RA**




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**Figure 6. Joint deformities**

**Syndromes in RA**

- SS (common): keratoconjunctivitis sicca and xerostomia (dry eyes and mouth)
- Caplan's syndrome (very rare): combination of RA + Pneumoconiosis that manifests as multiple intrapulmonary nodules
- Felty's syndrome (rare): arthritis, splenomegaly, neutropenia

## Investigations

- blood work
  - RF: 80% sensitivity but non-specific; may not be present at onset of symptoms; levels do not correlate with disease activity
    - can be associated with more erosions, more extra-articular manifestations, and worse function
  - anti-CCP: 80% sensitivity but more specific (94-98%); may precede onset of symptoms
  - increased disease activity is associated with decreased Hb (anemia of chronic disease), increased platelets, ESR, CRP, and RF
- imaging
  - bilateral hands/wrists, ankles/feet x-ray
    - first change is periarticular osteopenia, followed by erosions
  - C-spine x-ray (may be normal at onset, required for pre-operative assessment in long standing disease)
  - U/S (with power doppler) – often changes of synovitis/erosion noted in advance of those seen on plain x-ray
  - MRI may be used to image hands to detect early synovitis and erosions
  - MRI T1 inflamed synovium is hypointense and hyperintense on T1; bone marrow edema can be seen as well as areas of increased uptake gadolinium contrast



Poor prognostic features of RA include: young age of onset, high RF titer, elevated ESR, activity of >20 joints, and presence of extra-articular features



**Side Effects of Steroids**

- Weight gain
- Osteoporosis
- AVN
- Cataracts, glaucoma
- PUD
- Susceptibility to infection
- Easy bruising
- Acne
- HTN
- Hyperlipidemia
- Hypokalemia, hyperglycemia
- Mood swings

## Treatment

- goals of therapy: remission or lowest possible disease activity
  - key is early diagnosis and early intervention with DMARDs
  - "window of opportunity" = early treatment within first 3 mo of disease may allow better control/remission
  - assess poor prognostic factors at baseline (RF positive, functional limitations, and extra-articular features)
- behavioural
  - exercise program: active, gentle ROM and isometric exercise during flares; aquatic/aerobic/strengthening exercise between flares
  - job modification, assistive devices as necessary
  - interventions to reduce cardiovascular disease, smoking cessation, lipid control
- pharmacologic: alter disease progression
  - DMARDs and biologics (not analgesics or NSAIDs) can alter the course of RA
  - DMARDs
    - treatment with DMARDs should be started as soon as RA diagnosis is made, and should be aimed at reaching sustained remission
    - methotrexate (MTX) is the gold standard and is first-line unless contraindicated
      - chest X-ray should be assessed prior to MTX therapy
      - monitor every 3 mo, if inadequate response (3-6 mo) → combine or switch
      - consider including add-on medications to MTX if patients have poor prognostic features or high disease activity
      - add-ons include: hydroxychloroquine, sulfasalazine, leflunomide, biologics
      - if contraindication to MTX, hydroxychloroquine, sulfasalazine and/or leflunomide, should be considered with the former being considered as a weaker agent and the latter as more potent
  - biologics (bDMARD)
    - should be used if inadequate response to DMARDs
    - should be combined with DMARD therapy (initiating with combination therapy is associated with faster response rates and longer duration of effect)
    - first-line (anti-TNF) options: infliximab, etanercept, adalimumab, golimumab, and certolizumab
    - non anti-TNF agents include anakinra (almost never ued for RA), abatacept, rituximab, and tocilizumab
    - reassess every 3-6 mo and monitor disease activity (predominantly via assessing swollen joint count)
- pharmacologic: supportive to reduce inflammation and pain
  - NSAIDs
    - individualize according to efficacy and tolerability
    - contraindicated/cautioned in some patients (e.g. PUD, ischemic cardiac disease, pregnancy)
    - add acetaminophen for synergistic pain control
  - corticosteroids
    - local: injections to control symptoms in a specific joint
    - systemic (prednisone)
      - low dose (5-10 mg/d) useful for short-term to improve symptoms if NSAIDs are ineffective and to bridge gap until DMARDs take effect
      - can try DepoMedrol® with potential same effect as oral prednisone
      - severe RA: add low dose prednisone to DMARDs
      - do baseline DEXA bone density scan and consider bone supportive pharmacologic therapy if using corticosteroids >3 mo at 7.5 mg/d, particularly in those with other risk factors
      - cautions/contraindications: active infection, TB, osteoporosis, HTN, gastric ulcer, DM
- surgical
  - indicated for structural joint damage
  - surgical options include: synovectomy, joint replacement, joint fusion, reconstruction/tendon repair



DMARDs, prednisone and biologics alter the course of RA but not analgesics or NSAIDs

### Follow-Up Management and Clinical Outcomes

- clinical reassessment every 3-6 mo, then 6-12 mo after inflammation has been suppressed
- examine joints for active inflammation – if active, consider adjusting medications, PT/OT
- RA patients should be screened and managed for cardiovascular disease given increased risk
- if assessment reveals joint damage – consider analgesia, referral to PT/OT, surgical options
- outcome depends on disease activity, joint damage, physical functional status, psychological health, and comorbidities
- functional capacity is a useful tool for determining therapeutic effectiveness; many tools for evaluation have been validated
- patients with RA have an increased prevalence of other serious illnesses: infection (e.g. pulmonary, skin, joint), renal impairment, lymphoproliferative disorders, cardiovascular disease (correlates with disease activity and duration)
- risk of premature mortality, decreased life expectancy (most mortality not directly caused by RA)

## Systemic Lupus Erythematosus

- see Nephrology, NP23

### Definition

- chronic inflammatory multi-system disease of unknown etiology
- characterized by production of autoantibodies and diverse clinical manifestations

**Table 14. Diagnostic Criteria of SLE***

| Criteria | Description |
|---|---|
| **CLINICAL** | |
| Malar rash | Classic "butterfly rash", sparing of nasolabial folds, no scarring |
| Discoid rash | May cause scarring due to invasion of basement membrane |
| Photosensitivity | Skin rash in reaction to sunlight |
| Oral/nasal ulcers | Usually painless |
| Arthritis | Symmetric, involving ≥2 small or large peripheral joints, non-erosive |
| Serositis | Pleuritis or pericarditis |
| Neurologic disorder | Headache, seizures or psychosis, peripheral neuropathies |
| **LABORATORY** | |
| Renal disorder | Proteinuria (>0.5 g/d or 3+) |
| | Cellular casts (RBC, Hb, granular, tubular, mixed) |
| Hematologic disorder | Hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia |
| Immunologic disorder | Anti-dsDNA or anti-Sm or antiphospholipid Ab (anticardiolipin Ab, SLE anticoagulant) or false positive VDRL with 6 mo confirmatory negative |
| ANA | Most sensitive test (98%), not specific, ruling out SLE when negative |

*Note: "4, 7, 11" rule → 4 (or more) out of 11 criteria (4 lab, 7 clinical) must be present, serially or simultaneously, for diagnosis
American College of Rheumatology, 1997 update

**Diagnostic Criteria of SLE**

**MD SOAP BRAIN**
**M**alar rash
**D**iscoid rash
**S**erositis
**O**ral ulcers
**A**NA
**P**hotosensitivity
**B**lood
**R**enal
**A**rthritis
**I**mmune
**N**eurologic

### Etiology and Pathophysiology

- production of cytotoxic autoantibodies and immune complex formation
- multi-factorial etiology
- **genetics**
  - common association with HLA-B8/DR3; ~10% have positive family history
  - strong association with defects in apoptotic clearance → fragments of nuclear particles captured by antigen-presenting cells → develop anti-nuclear antibodies
  - cytokines involved in inflammatory process and tissue injury: B-lymphocyte stimulator (BlyS), IL-6, IL-17, IL-18, TNF-α
- **environment**
  - UV radiation, cigarette smoking, infection, vitamin D deficiency
- **estrogen**
  - increased incidence after puberty, decreased incidence after menopause
  - men with SLE have higher concentration of estrogenic metabolites
- **infection**
  - viral (non-specific stimulant of immune response)
- **drug-induced**
  - anti-hypertensives (hydralazine), anti-convulsants (phenytoin), anti-arrhythmics (procainamide), isoniazid, biologics, oral contraceptive pills
  - anti-histone Abs are commonly seen in drug-induced SLE
  - symptoms resolve with discontinuation of offending drug

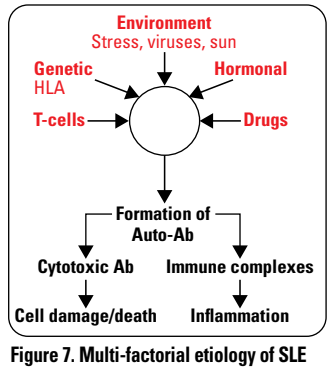



**Figure 7. Multi-factorial etiology of SLE**

**Drug-Induced SLE**
Often presents atypically with systemic features and serositis; usually associated with anti-histone Ab

## Epidemiology
- prevalence: 0.05% overall
- F:M = 10:1
- age of onset in reproductive yr (13-40)
- more common and severe in African-Americans and Asians
- bimodal mortality pattern
  - early (within 2 yr)
    - active SLE, active nephritis, infection secondary to steroid use
  - late (>10 yr)
    - inactive SLE, inactive nephritis, atherosclerosis likely due to chronic inflammation

## Signs and Symptoms
- characterized by periods of exacerbation and remission

**Table 15. Signs and Symptoms of SLE**

| System | Symptoms |
|---|---|
| **Systemic** | Fatigue, malaise, weight loss, fever, lymphadenopathy |
| **Renal** | Hematuria, proteinuria (glomerulonephritis), HTN, peripheral edema, renal failure |
| **Dermatologic** | Photosensitivity, malar rash, discoid rash, oral ulcers, alopecia (hair loss), purpura, panniculitis (inflammation of subcutaneous fat and muscle tissue), urticaria |
| **Musculoskeletal** | Polyarthralgias, polyarthritis, myalgias, AVN; reducible deformities of hand = Jaccoud's arthritis |
| **Ophthalmic** | Keratoconjunctivitis sicca, episcleritis, scleritis, cytoid bodies (cotton wool exudates on fundoscopy = infarction of nerve cell layer of retina) |
| **Cardiac** | Pericarditis, CAD, non-bacterial endocarditis (Libman-Sachs), myocarditis<br>Note: SLE is an independent risk factor for atherosclerosis and CAD |
| **Vascular** | Raynaud's phenomenon, livedo reticularis (mottled discolouration of skin due to narrowing of blood vessels, characteristic lacy or net-like appearance), thrombosis, vasculitis |
| **Respiratory** | Pleuritis, ILD, pulmonary HTN, PE, alveolar hemorrhage |
| **Gastrointestinal** | Pancreatitis, SLE enteropathy, hepatitis, hepatomegaly, splenomegaly |
| **Neurologic/Psychiatric** | H/A, depression, psychosis, seizures, cerebritis, transverse myelitis, peripheral neuropathy, stroke |
| **Life/Organ-Threatening** | Cardiac: coronary vasculitis, malignant HTN, tamponade<br>Hematologic: hemolytic anemia, neutropenia, thrombocytopenia, TTP, thrombosis<br>Neurologic: seizures, CVA, stroke<br>Respiratory: pulmonary hypertension, pulmonary hemorrhage, emboli |

**Raynaud's Phenomenon**
Vasospastic disorder characteristically causing discolouration of fingers and toes (white → blue → red)
Classic triggers: cold and emotional stress

## Investigations
- ANA (98% sensitivity, but poor specificity → used as a screening test; ANA titres are not useful to follow disease course)
- anti-dsDNA and anti-Sm are specific (95-99%)
- anti-dsDNA titre and serum complement (C3, C4) are useful to monitor treatment response in patients who are clinically and serologically concordant (anti-dsDNA, C3, and C4 also fluctuate with disease acitivity)
- antiphospholipid Ab (anti-cardiolipin Ab, SLE anticoagulant, anti-β2 glycoprotein-I Ab), may cause increased risk of clotting and increased aPTT

Consider SLE in a patient who has involvement of 2 or more organ systems

## Treatment
- **goals of therapy**
  - usually immunosuppressive ± corticosteroid
  - treat early and avoid long-term steroid use, if unavoidable see Endocrinology, E44 for osteoporosis management
  - if high doses of steroids necessary for long-term control, add steroid-sparing agents and taper when possible
  - treatment is tailored to organ system involved and severity of disease
  - all medications used to treat SLE require periodic monitoring for potential toxicity
- **dermatologic**
  - sunscreen, avoid UV light and estrogens
  - topical steroids, hydroxychloroquine
- **musculoskeletal**
  - NSAIDs ± gastroprotective agent for arthritis (also beneficial for pleuritis and pericarditis)
  - hydroxychloroquine improves long-term control and prevents flares
  - bisphosphonates, calcium, vitamin D to combat osteoporosis
- **organ-threatening disease**
  - high-dose oral prednisone or IV methylprednisolone in severe disease
  - steroid-sparing agents: azathioprine, MTX, mycophenolate (can use mofetil or sodium)
  - IV cyclophosphamide for serious organ involvement (e.g. cerebritis or lupus nephritis) for clinical features of lupus nephritis

The arthritis of SLE can be deforming but it is non-erosive (in contrast to RA)

# Antiphospholipid Antibody Syndrome

## Definition

- multi-system vasculopathy manifested by recurrent thromboembolic events, spontaneous abortions, and thrombocytopenia
- circulating antiphospholipid autoantibodies interfere with coagulation
- **primary APLS**: occurs in the absence of other disease
- **secondary APLS**: occurs in the setting of a connective tissue disease (including SLE), malignancy, drugs (hydralazine, procainamide, phenytoin, interferon, quinidine), and infections (HIV, TB, hepatitis C, infectious mononucleosis)
- **catastrophic APLS**: development within 1 wk of small vessel thrombotic occlusion in ≥3 organ systems with positive antiphospholipid Ab (high mortality)

**Table 16. Classification Criteria of APLS***

| Criteria | Description |
|---|---|
| **CLINICAL** | |
| Vascular thrombosis | Arterial: stroke/TIA, multi-infarct dementia, MI, valvular incompetence, limb ischemia |
| | Venous: DVT, PE, renal and retinal vein thrombosis |
| | Must be confirmed by imaging or histopathology |
| Pregnancy morbidity | Recurrent spontaneous abortions (<10 wk GA) , fetal death (>10 wk GA), or premature birth (<34 wk GA) |
| **LABORATORY** | Labs must be positive on 2 occasions, at least 12 wk apart |
| Lupus anticoagulant | Prolonged aPTT not corrected by the addition of normal plasma |
| Anti-cardiolipin Ab | IgG and/or IgM |
| Anti-β2 glycoprotein-I Ab | IgG and/or IgM |
| ANA | Most sensitive test (98%), not specific |

* 1 clinical and 1 laboratory criteria must be present J Thromb Haemost 2006;4:295-306

**Manifestations of APLA**
- Thromboembolic events
- Spontaneous abortions
- Thrombocytopenia
- Associated with livedo reticularis, migraine headaches

## Signs and Symptoms

- see Clinical Criteria in Table 16
- hematologic
  - thrombocytopenia, hemolytic anemia, neutropenia
- dermatologic
  - livedo reticularis, Raynaud's phenomenon, purpura, leg ulcers, and gangrene

Arterial and venous thrombosis are usually mutually exclusive

## Treatment

- thrombosis
  - lifelong anti-coagulation with warfarin
  - target INR 2.0-3.0 for first venous event, >3.0 for recurrent and/or arterial event
- recurrent fetal loss
  - heparin/low molecular weight heparin ± ASA during pregnancy
- catastrophic APLS
  - high-dose steroids, anti-coagulation, cyclophosphamide, plasmapheresis

# Scleroderma (i.e. Systemic Sclerosis)

## Definition

- a non-inflammatory autoimmune disorder characterized by widespread small vessel vasculopathy, production of autoantibodies, and fibroblast dysfunction causing fibrosis

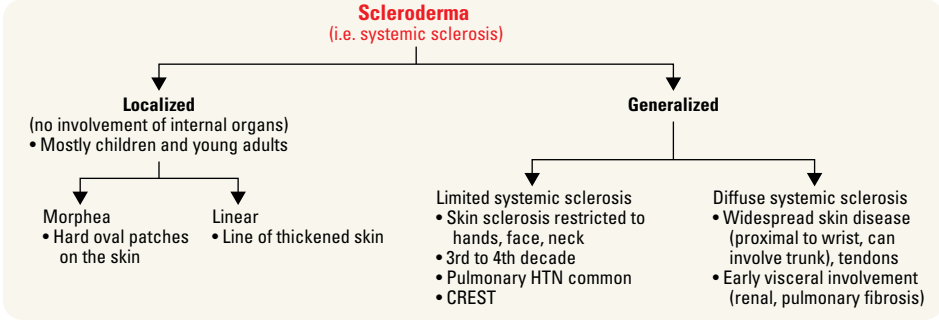



**Figure 8. Forms of scleroderma**

**CREST Syndrome**
**C**alcinosis
**R**aynaud's phenomenon
**E**sophageal dysmotility
**S**clerodactyly
**T**elangiectasia

Scleroderma is the most common cause of secondary Raynaud's phenomenon

**Table 17. The American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Criteria for Scleroderma***

| Item | Sub-item | Score |
|---|---|---|
| 1. Skin thickening of fingers of both hands extending proximal to the MCP (sufficient criterion) | | 9 |
| 2. Skin thickening of the fingers | Puffy fingers<br>Sclerodactyly | 2<br>4 |
| 3. Fingertip lesions | Digital tip ulcers<br>Fingertip pitting scars | 2<br>3 |
| 4. Telangiectasia | | 2 |
| 5. Abnormal nailfold capillaries | | 2 |
| 6. Pulmonary arterial HTN ± ILD (max score 2) | Pulmonary arterial HTN<br>ILD | 2<br>2 |
| 7. Raynaud's phenomenon | | 3 |
| 8. Scleroderma related Ab | Anti-centromere<br>Anti-topoisomerase I<br>Anti-RNA polymerase III | 3 |

* Score of ≥9 is sufficient to classify a patient as having definite scleroderma (sensitivity 0.95, specificity 0.93)
Arthritis & Rheum 2013;65(11):2737-2747

**Cyclophosphamine versus Placebo in Scleroderma Lung Disease**
NEJM 2006; 354:2655-66
**Study**: Double-blind, randomized, placebo-controlled trial.
**Study**: Lung function and health-related symptoms.
**Results**: The mean absolute difference in adjusted 12 mo FVC percent predicted between cyclophosphamide and placebo groups was 2.53 percent, favouring cyclophosphamide. There were also treatment-related differences in physiological and symptom outcomes, and the difference in FVC was maintained at 24 mo.
**Conclusion**: Cyclophosphamide has a significant but modest beneficial effect on lung function, dyspnea, thickening of skin, and health-related quality of life in patients with symptomatic, scleroderma-related interstitial lung disease.

## Etiology and Pathophysiology

- idiopathic vasculopathy (not vasculitis) leading to atrophy and fibrosis of tissues
  - intimal proliferation and media mucinous degeneration → progressive obliteration of vessel lumen → fibrotic tissue
  - resembles malignant HTN
  - lung disease is the most common cause of morbidity and mortality

## Epidemiology

- F:M = 3-4:1, peaking in 5th decades
- associated with HLA-DR1 and environmental exposures (silica, epoxy resins, toxic oil, aromatic hydrocarbons, polyvinyl chloride)
- limited systemic sclerosis has a higher survival prognosis (>70% at 10 yr) than diffuse systemic sclerosis (40-60% at 10 yr)

**Raynaud's Phenomenon DDx**

**COLD HAND**
**C**ryoglobulins/**C**ryofibrinogens
**O**bstruction/**O**ccupational
**L**upus erythematosus, other connective tissue disease
**D**iabetes mellitus/**D**rugs
**H**ematologic problems (polycythemia, leukemia, etc.)
**A**rterial problems (atherosclerosis)/**A**norexia nervosa
**N**eurologic problems (vascular tone)
**D**isease of unknown origin (idiopathic)

## Signs and Symptoms

**Table 18. Clinical Manifestations of Scleroderma**

| System | Features |
|---|---|
| **Dermatologic** | Painless non-pitting edema → skin tightening<br>Ulcerations, calcinosis, periungual erythema, hypo/hyperpigmentation, pruritus, telangiectasias<br>Characteristic face: mask-like facies with tight lips, beak nose, radial perioral furrows |
| **Vascular** | Raynaud's phenomenon → digital pits, gangrene |
| **Gastrointestinal (~90%)** | Distal esophageal hypomotility → dysphagia<br>Loss of lower esophageal sphincter function → GERD, ulcerations, strictures<br>Small bowel hypomotility → bacterial overgrowth, diarrhea, bloating, cramps, malabsorption, weight loss<br>Large bowel hypomotility → wide mouth diverticuli are pathognomonic radiographic finding on barium study |
| **Renal** | Mild proteinuria, Cr elevation, HTN<br>"Scleroderma renal crisis" (10-15%) may lead to malignant arterial HTN, oliguria, and microangiopathic hemolytic anemia |
| **Pulmonary** | Interstitial fibrosis, pulmonary HTN, pleurisy, pleural effusions |
| **Cardiac** | Left ventricular dysfunction, pericarditis, pericardial effusion, arrhythmias |
| **Musculoskeletal** | Polyarthralgias<br>"Resorption of distal tufts" (radiological finding)<br>Proximal weakness 2° to disuse, atrophy, low grade myopathy |
| **Endocrine** | Hypothyroidism |

**Features of Pathologic Raynaud's Syndrome**
- New onset
- Asymmetric
- Precipitated by stimuli other than cold or emotion
- Associated with distal pulp pitting or tissue reabsorption
- Digit ischemia
- Capillary dilatation by capillaroscopy

## Investigations

- blood work
  - CBC, Cr, ANA
  - anti-topoisomerase 1/anti-Scl-70: specific but not sensitive for diffuse systemic sclerosis
  - anti-centromere: favours diagnosis of CREST (limited systemic sclerosis)
- PFT
  - assess for interstitial lung disease
- imaging
  - CXR for fibrosis, echo for pulmonary HTN

### Treatment
- dermatologic
  - good skin hygiene
  - low-dose prednisone (>20 mg may provoke renal crisis if susceptible), MTX (limited evidence)
- vascular
  - patient education on cold avoidance
  - vasodilators (CCBs, local nitroglycerine cream, systemic PGE2 inhibitors, PDE5 inhibitors)
- gastrointestinal
  - GERD: PPIs are first-line, then H2-receptor agonists
  - small bowel bacterial overgrowth: broad spectrum antibiotics (tetracycline, metronidazole)
- renal disease
  - ACE inhibitor for hypertensive crisis
  - see Nephrology, NP32 for scleroderma renal crisis
- pulmonary
  - early interstitial disease: mycophenolate mofetil (less toxicity) or cyclophosphamide
  - pulmonary HTN: vasodilators (e.g. bosentan , epoprostenol, and PDE5 inhibitors)
  - rapidly progressive disease at risk of organ failure: consider hematopoietic stem cell transplantation
- cardiac
  - pericarditis: systemic steroids
- musculoskeletal
  - arthritis: NSAIDs
  - myositis: systemic steroids

## Idiopathic Inflammatory Myopathy

### Definition
- autoimmune diseases characterized by proximal muscle weakness ± pain
- muscle becomes damaged by a non-suppurative lymphocytic inflammatory process
- associated with malignancy
  - increased risk of malignancy: age >50, DMM>PM, normal CK, refractory disease
- associated with other connective tissue disease, Raynaud's phenomenon, autoimmune disorders

### Classification
- PM/DMM
- adult and juvenile form

### Inclusion Body Myositis
- age >50, M>F, slowly progressive, vacuoles in cells on biopsy
- suspect when patient unresponsive to treatment
- distal as well as proximal muscle weakness
- muscle biopsy positive for inclusion bodies

### POLYMYOSITIS/DERMATOMYOSITIS

**Table 19. Classification Criteria for PM/DMM***

| Criteria | Description |
|---|---|
| 1. Symmetric proximal muscle weakness (usually progressive) | Typical involvement of shoulder girdle and hip girdle<br>Dysphagia or esophageal dysmotility |
| 2. Elevated muscle enzymes | ↑ CK, aldolase, LDH, AST, ALT |
| 3. EMG changes | Short polyphasic motor units, high frequency repetitive discharge, insertional irritability |
| 4. Muscle biopsy | DMM: peripheral round cell infiltrate into fascicle with necrosis, complement and pos. immunofluorescence; PM: round cell infiltrate in fascicle with necrotic or regenerating fibres throughout muscle bundle |
| 5. Typical rash of dermatomyositis | Required for diagnosis of DMM (see below) |

*Definite if 4 present, probable if 3 present NEJM 1975;292:403-407

**Signs of DMM**
Gottron's papules and Gottron's sign are pathognomonic of DMM (occur in 70% of patients)

### Etiology and Pathophysiology
- PM is CD8 cell-mediated muscle necrosis, found in adults
- DMM is B-cell and CD4 immune complex-mediated, and causes peri-fascicular vascular abnormalities

### Signs and Symptoms

- progressive symmetrical proximal muscle weakness (shoulder and hip) developing over weeks to months
  - difficulty lifting head off pillow, arising from chair, climbing stairs
- dermatological
  - DMM has characteristic dermatological features (F>M, children and adults)
    - Gottron's papules
      - pink-violaceous, flat-topped papules overlying the dorsal surface of the interphalangeal joints
    - Gottron's sign
      - erythematous, smooth or scaly patches over the dorsal IPs, MCPs, elbows, knees, or medial malleoli
    - heliotrope rash: violaceous rash over the eyelids; usually with edema
    - shawl sign: poikilodermatous erythematous rash over neck, upper chest, and shoulders
    - mechanic's hands: dry, crackled lesions on palmar and lateral surface of digits, especially over the pulp space
    - periungual erythema
- cardiac
  - arrhythmias, CHF, conduction defect, ventricular hypertrophy, pericarditis
- gastrointestinal
  - oropharyngeal and lower esophageal dysphagia, reflux
- pulmonary
  - weakness of respiratory muscles, ILD, aspiration pneumonia

**Malignancies Associated with DMM**
- Breast
- Lung
- Colon
- Ovarian

### Investigations

- blood work: CK, ANA, anti-Jo-1 (DMM), anti-Mi-2, anti-SRP
- imaging: MRI may be used to localize biopsy site
- EMG: characteristic findings of muscle inflammation and damage
  - muscle biopsy can aid in diagnosis, however not needed in those with classic skin findings and muscle weakness

**Classic Triad (identifies 93% of Sjögren's patients)**
- Dry eyes
- Dry mouth (xerostomia) → dysphagia
- Arthritis (small joint, asymmetrical, non-erosive) but may be associated with rheumatoid arthritis, in which case, the arthritis is erosive and symmetric

### Treatment

- non-pharmacological treatment
  - physical therapy and occupational therapy, speech language therapy for esophageal dysfunction
- pharmacological treatment
  - high-dose corticosteroid (1-2 mg/kg/d) usually not exceeding 80 mg daily and slow taper
  - add immunosuppressive agents (azathioprine, MTX)
  - IVIg if severe or refractory
  - hydroxychloroquine for DMM rash
- malignancy surveillance
  - detailed history and physical (breast, pelvic, and rectal exam)
  - CXR, abdominal and pelvic U/S, fecal occult blood, Pap test, mammogram ± CT scan (thoracic, abdominal, pelvic)

## Sjögren's Syndrome

### Definition

- autoimmune condition characterized by dry eyes (keratoconjunctivitis sicca/xerophthalmia) and dry mouth (xerostomia), caused by lymphocytic infiltration of salivary and lacrimal glands
- may evolve into systemic disorder (20%) with diminished exocrine gland activity in respiratory tract and skin
- primary and secondary form (associated with RA, SLE, DMM, and HIV)
- prevalence 0.5%, F>>M 10:1, 40-60 yr
- increased risk of non-Hodgkin's lymphoma (lifetime incidence 6-7%)

**Table 20. The American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Criteria for Primary Sjögren's Syndrome (no condition in exclusion criteria, score ≥6)**

| Criteria | Score | Comments |
|---|---|---|
| Labial salivary gland biopsy with focal lymphocytic sialadenitis with focus score ≥1 focus /4mm$^2$ | 3 | Focus scores are histopathologic grading systems<br>Strongly associated with phenotypic ocular and serological components of Sjögren's |
| Anti-SSA or Ro positive | 3 | |
| Ocular staining score ≥5 (or van Bijsterfeld score ≥4 on at least one eye | 1 | Ocular staining score based on fluorescein dye examination of conjunctiva and cornea to determine clinical changes |
| Schirmer's test ≤5 mm / 5 min on at least one eye | 1 | |
| Unstimulated whole saliva flow rate ≤0.1 mL/min | 1 | |
| Exclusion criteria include prior diagnosis of any of the following conditions: 1) history of head and neck radiation treatment, 2) active hepatitis C infection (with confirmation by polymerase chain reaction, 3) AIDS, 4) sarcoidosis, 5) amyloidosis, 6) graft-versus-host disease, 7) IgG4-related disease | | |

Arthritis Rheumatol. 2017;69:35-45

### Signs and Symptoms

- "sicca complex": dry eyes (keratoconjunctivitis sicca/xerophthalmia), dry mouth (xerostomia), complicated by staphylococcal blepharitis
- dental caries, oral candidiasis, angular cheilitis (inflammation and fissuring at the labial commissures of the mouth)
- systemic complications
  - sinusitis
  - autoimmune thyroid dysfunction
  - arthralgias, arthritis
  - subclinical diffuse ILD, xerotrachea leading to chronic dry cough
  - renal disease, glomerulonephritis
  - palpable purpura, vasculitis
  - peripheral neuropathy
  - lymphoma risk greatly increased

### Treatment

- ocular
  - artificial tears/ tear gel if severe, or surgical punctal occlusion for dry eyes
- oral
  - good dental hygiene, hydration
  - parasympathomimetic agents that stimulate salivary flow (e.g. pilocarpine)
  - topical nystatin or clotrimazole x 4-6 wk for oral candidiasis
- systemic (e.g. hydroxychloroquine, corticosteroids), Rituximab can be used in severe disease

## Mixed Connective Tissue Disease

- syndrome with features of 3 different connective tissue diseases (e.g. SLE, scleroderma, PM)
- common symptoms: Raynaud's phenomenon, swollen fingers
- blood work: anti-RNP (see Table 10)
- treatment is generally guided by the severity of symptoms and organ system involvement
- prognosis
  - 50-60% will evolve into SLE
  - 40% will evolve into scleroderma
  - only 10% will remain as MCTD for the rest of their lives
  - cardiac involvement (arrhythmia) common, renal or lung involvement rare

## Overlap Syndrome

- syndrome with sufficient diagnostic features of 2+ different connective tissue diseases

# Vasculitides

- inflammation and subsequent necrosis of blood vessels leading to tissue ischemia or infarction of any organ system
- diagnosis
  - clinical suspicion: suspect in cases of unexplained multiple organ ischemia or systemic illness with no evidence of malignancy or infection; constitutional symptoms such as fever, weight loss, anorexia, fatigue
  - labs non-specific: anemia, increased WBC and ESR, abnormal U/A
  - investigations: biopsy if tissue accessible; angiography if tissue inaccessible
- treatment generally involves corticosteroids and/or immunosuppressive agents

**Features of Small Vessel Vasculitis**
- Palpable purpura
- Vesicles
- Chronic urticaria
- Superficial ulcers (erosions)

**Table 21. Classification of Vasculitis and Characteristic Features**

| Classification | Characteristic Features |
|---|---|
| **SMALL VESSEL** | |
| Non-ANCA-associated | Immune complex-mediated (most common mechanism) |
| Anti-GBM (Goodpasture's disease) | Autoantibodies targeting type IV collagen in both glomerular basement membrane and alveoli causing glomerulonephritis and/or pulmonary findings |
| Anti-C1q vasculitis (Hypocomplementemic urticarial vasculitis syndrome) | Specific autoimmune disorder with at least 6 mo of urticaria with C1q complement deficiency with various systemic findings |
| Predominantly cutaneous vasculitis | Also known as hypersensitivity/leukocytoclastic vasculitis |
| IgA vasculitis (formely Henoch-Schönlein purpura [HSP]) (see Pediatrics, P88) | Vascular deposition of IgA causing systemic vasculitis (skin, GI, renal), usually self-limiting; most common in childhood |
| Cryoglobulinemic vasculitis (CV) | Systemic vasculitis caused by circulating cryoproteins forming immune complexes; 60-80% of cases are due to Hepatitis C, 5-10% are due to a CTD (SLE, RA, SS), 5-10% are due to a lymphoproliferative disorder and the remaining 5-10% are idiopathic or "essential". CV may be associated with underlying infection (e.g. hepatitis C) or connective tissue disease |
| ANCA-associated (i.e. PR3-ANCA) Granulomatosis with polyangiitis (GPA, formerly Wegener's) PR3 (c-ANCA) > MPO (p-ANCA) | Granulomatous inflammation of vessels of respiratory tract and kidneys; initially have URTI symptoms; most common in middle age |
| Eosinophilic granulomatosis with polyangiitis (EGPA), formerly Churg-Strauss syndrome) (50% ANCA positive) | Granulomatous inflammation of vessels with hypereosinophilia and eosinophilic tissue infiltration, frequent lung involvement (asthma, allergic rhinitis), associated with MPO-ANCA in 40-50% of cases. Other manifestations include peripheral neuropathy (70%), GI involvement, myocarditis, and rarely coronary arteritis; average age 40s |
| Microangiopathic polyangiitis (MPA) (70% ANCA positive, usually MPO) | Pauci-immune necrotizing vasculitis, affects kidneys (necrotizing glomerulonephritis), lungs (capillaritis and alveolar hemorrhage), skin; most common in middle age |
| **MEDIUM VESSEL** | |
| Polyarteritis nodosa | Segmental, non-granulomatous necrotizing inflammation<br>Unknown etiology in most cases, any age (average 40-50s), M>F |
| Kawasaki disease (see Pediatrics, P88) | Arteritis and mucocutaneous lymph node syndrome |
| **LARGE VESSEL** | |
| GCA/Temporal arteritis | Inflammation predominantly of the aorta and its branches<br>>50 yr of age, F>M |
| Takayasu's arteritis | "Pulseless disease", unequal peripheral pulses, chronic inflammation, most often the aorta and its branches<br>Most common in young adults of Asian descent, 10-40 yr of age, F>M, risk of aortic aneurysm |
| **OTHER VASCULITIDES** | |
| Buerger's disease ("Thromboangiits Obliterans") | Inflammation and clotting of small and medium-sized arteries and veins of distal extremities, may lead to distal claudication and gangrene, most important etiologic factor is cigarette smoking. Most common in young Asian males, M>F |
| Behçet's disease | Multi-system disorder presenting with ocular involvement (uveitis), recurrent oral and genital ulceration, venous thrombosis, skin and joint involvement; most common in Mediterranean and Asian populations, average age 30 yr old, M>F |
| Vasculitis mimicry (i.e. pseudovasculitis) | Cholesterol emboli, atrial myxoma, bacterial endocarditis (SBE), APLS |

**c-ANCA** (i.e. pR3-ANCA): cytoplasmic anti-neutrophil cytoplasmic Ab associated with anti-PR3
**p-ANCA** (i.e. MPO-ANCA): perinuclear anti-neutrophil cytoplasmic Ab associated with multiple antigens, e.g. myeloperoxidase, lactoferrin (IBD), cathepsin, elastase etc. Of these only antibodies to myeloperoxidase have been associated with the development of vasculitis

**Churg-Strauss Triad**
- Allergic rhinitis and asthma (often quiescent at time of vasculitis)
- Eosinophilic infiltrative disease resembling pneumonia
- Systemic vasculitis often mononeuritis multiplex/peripheral neuropathy and peripheral eosinophilia

**Features of Medium Vessel Vasculitis**
- Livedo reticularis
- Erythema nodosum
- Raynaud's phenomenon
- Nodules
- Digital infarcts
- Ulcers

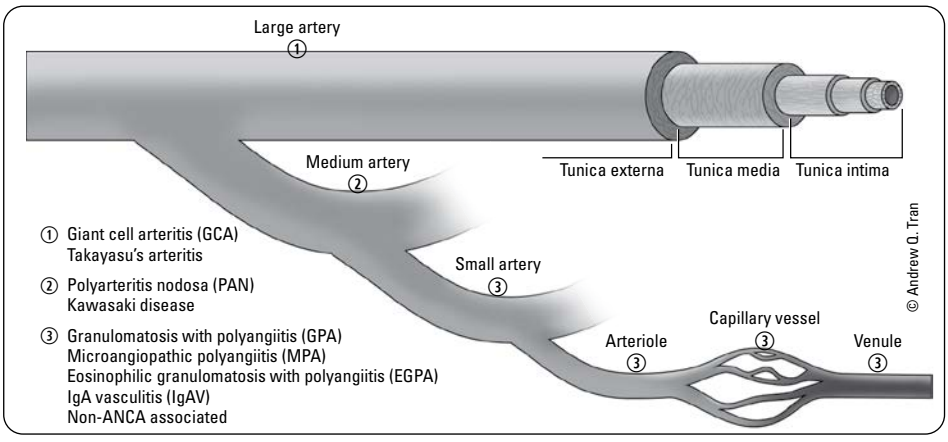



**Figure 9. Classification of vasculitides by vessel size**

# Small Vessel Non-ANCA Associated Vasculitis

## CUTANEOUS VASCULITIS

- subdivided into:
  - drug-induced vasculitis
  - serum sickness reaction
  - vasculitis associated with other underlying primary diseases (CTD, infections, malignancies – hematologic > solid tumours)

### Etiology and Pathophysiology

- cutaneous vasculitis following:
  - drug exposure (allopurinol, gold, sulfonamides, penicillin, phenytoin)
  - viral or bacterial infection
  - idiopathic causes
- small vessels involved (post-capillary venules most frequently)
- usually causes a leukocytoclastic vasculitis: debris from neutrophils around vessels
- sometimes due to cryoglobulins which precipitate in cold temperatures

### Signs and Symptoms

- palpable purpura ± vesicles and ulceration, urticaria, macules, papules, bullae, subcutaneous nodules
  - renal or joint involvement may occur, especially in children

### Investigations

- vascular involvement (both arteriole and venule) established by skin biopsy

### Treatment

- stop possible offending drug
- NSAID, low dose corticosteroids
  - immunosuppressive agents in resistant cases
- usually self-limiting

# Small Vessel ANCA-Associated Vasculitis

## GRANULOMATOSIS WITH POLYANGIITIS (GPA, formerly known as Wegener's Granulomatosis)

### Definition

- granulomatous inflammation of vessels that may affect the upper airways (rhinitis, sinusitis), lungs (pulmonary nodules, infiltrates), and kidneys (glomerulonephritis, renal failure)
- highly associated with c-ANCA by indirect immunofluorescence (IIF) and PR3-ANCA by ELISA; however, changes in ANCA levels do not predict remission or relapse
- incidence 2-3 per 100,000; more common in Northern latitudes

**Table 22. Classification Criteria for GPA***

| Criteria | Description |
|---|---|
| 1. Nasal or oral involvement | Inflammation, ulcers, epistaxis |
| 2. Abnormal findings on CXR | Nodules, cavitations, etc. |
| 3. Urinary sediment | Microscopic hematuria ± RBC casts |
| 4. Biopsy of involved tissue | Lungs show granulomas, kidneys show necrotizing segmental glomerulonephritis |

*Diagnosed if 2 or more of the above 4 criteria present American College of Rheumatology, 1990

**Classic Features of GPA**
- Necrotizing granulomatous vasculitis of lower and upper respiratory tract
- Focal segmental glomerulonephritis

### Etiology
- pathogenesis depends on genetic susceptibility and environmental triggers (e.g. infection)
  - dysregulated immune response due to loss of B and T cell tolerance
  - acute vascular injury mediated by neutrophils and monocytes

### Signs and Symptoms
- systemic
  - malaise, fever, weakness, weight loss
- HEENT
  - sinusitis or rhinitis, nasal crusting and bloody nasal discharge, nasoseptal perforation, saddle nose deformity
  - proptosis due to: inflammation/vasculitis involving extra-ocular muscles, granulomatous retrobulbar space occupying lesions or direct extension of masses from the upper respiratory tract
  - hearing loss due to involvement of CN VIII
- pulmonary
  - cough, hemoptysis, granulomatous upper respiratory tract masses, tracheal and bronchial stenosis
- renal
  - hematuria, proteinuria, elevated creatinine, glomerulonephritis
- other
  - joint, skin, eye complaints, vasculitic neuropathy

### Investigations
- blood work: anemia (normal MCV), increased WBC, increased Cr, increased ESR, elevated platelet count, ANCA (PR3 > MPO)
- urinalysis: proteinuria, hematuria, RBC casts
- CXR: pneumonitis, lung nodules, infiltrations, cavitary lesions
- biopsy for confirmation of disease: skin, renal (segmental necrotizing glomerulonephritis), lung (vasculitis, necrosis)
- ESR and/or CRP may be used to monitor response to treatment in some patients

### Treatment
- for severe, life or organ threatening disease
  - pulse methylprednisolone 0.5-1.0 g/d x 1-3 d followed by prednisone 1 mg/kg/d PO + cyclophosphamide 2 mg/kg/d PO for 3-6 mo OR rituximab 375 mg/m$^2$ x 4 weekly infusions followed by high dose MTX (20-25 mg PO/SC weekly) or azathioprine (2 mg/kg/d PO OD)
- plasma exchange is usually not recommended as it does not reduce mortality nor end stage renal disease

**Efficacy of Remission Induction Regimens for ANCA-Associated Vasculitides (RAVE) Trial**
NEJM 2013; 369:417-427
**Study**: Multicentre, randomized, double-blind, double-dummy, non-inferiority trial.
**Intervention**: Rituximab
**Outcome**: Complete remission of disease by 6 mo, with remission maintained through 18 mo.
**Results**: 64% of the patients in the rituximab group, as compared with 53% of the patients in the cyclophosphamide–azathioprine group, had a complete remission by 6 mo. At 12 and 18 mo, 48% and 39%, respectively, of the patients in the rituximab group maintained complete remission, as compared with 39% and 33%, respectively, in the comparison group. Rituximab met the prespecified criteria for noninferiority. There was no significant difference between the groups in any efficacy measure, including the duration of complete remission and the frequency or severity of relapses. Among the 101 patients who had relapsing disease at baseline, rituximab was superior to conventional immunosuppression at 6 mo (P=0.01) and at 12 mo (P=0.009) but not at 18 mo.
**Conclusion**: In patients with severe ANCA-associated vasculitis, a single course of rituximab was as effective as continuous conventional immunosuppressive therapy for the induction and maintenance of remission over the course of 18 mo.

# Medium Vessel Vasculitis

## POLYARTERITIS NODOSA (PAN)

### Definition
- systemic, necrotizing vasculitis of medium sized vessels
- ANCA negative, classically lung-sparing
- 5-10% associated with hepatitis B positivity
- incidence 0.7 per 100,000; affects individuals between 40-60 yr; M:F = 2:1

**Table 23. Classification Criteria for PAN***

| Criteria | Description |
|---|---|
| 1. Weight loss | ≥4 kg, not due to dieting or other factors |
| 2. Myalgias, weakness, or leg tenderness | Diffuse myalgias or muscle weakness |
| 3. Livedo reticularis | Mottled, reticular pattern over skin |
| 4. Neuropathy | Mononeuropathy, mononeuropathy multiplex, or polyneuropathy |
| 5. Testicular pain or tenderness | Not due to infection, trauma, or other causes |
| 6. dBP >90 mmHg | Development of HTN with dBP >90 mmHg |
| 7. Elevated Cr or BUN | Cr >130 µmol/L (1.5 mg/dL), BUN >14.3 mmol/L (40 mg/dL) |
| 8. Hepatitis B positive | Presence of hepatitis B surface antigen or Ab |
| 9. Arteriographic abnormality | Commonly aneurysms |
| 10. Biopsy of artery | Presence of granulocytes and/or mononuclear leukocytes in the artery wall |

*Diagnosed if 3 or more of the above 10 criteria present  American College of Rheumatology, 1990

### Signs and Symptoms
- systemic: fatigue, weight loss, weakness, fever, arthralgias
- dermatologic: livedo reticularis, nodules, purpura, eruptions
- renal: renal insufficiency leading to HTN
- neuro: Mononeuropathy multiplex in both motor and sensory nerves
- abdo: abdominal pain, mesenteric arteritis

### Etiology and Pathophysiology
- focal panmural necrotizing inflammatory lesions in small and medium-sized arteries
- thrombosis, aneurysm, or dilatation at lesion site may occur
- healed lesions show proliferation of fibrous tissue and endothelial cells that may lead to luminal occlusion

### Investigations
- blood work: CBC, ESR, Cr, BUN, p-ANCA, hepatitis B serology
- imaging: angiography
- arterial biopsy

### Treatment
- prednisone 1 mg/kg/d PO (max 60 mg/d) ± and cyclophosphamide 2 mg/kg/d PO (max 200 mg/d) followed by azathioprine (2 mg/kg/d) or MTX (20-25 mg/kg/w) for remission maintenance; total treatment duration (18 mo)
- ± anti-viral therapy to enhance clearance of hepatitis B virus

## Large Vessel Vasculitis

### GCA/TEMPORAL ARTERITIS

**Table 24. Classification Criteria for GCA***

| Criteria | Description |
|---|---|
| 1. Age at onset ≥50 | |
| 2. New H/A | Often temporal |
| 3. Temporal artery abnormality | Temporal artery tenderness or decreased pulsations, not due to arteriosclerosis |
| 4. Elevated ESR | ESR ≥50 mm/h |
| 5. Abnormal artery biopsy | Mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells |

*Diagnosed if 3 or more of the above 5 criteria present American College of Rheumatology, 1990

**GCA Criteria**
Presence of 3 or more criteria yields sensitivity of 94%, specificity of 91%

### Epidemiology
- most frequent vasculitis in North America
- patients >50 yr; peak incidence 70-80 yr
- F:M = 2:1
- North-South gradient (predominance in Northern Europe/US)
- affects extracranial arteries

### Signs and Symptoms
- new onset temporal H/A ± scalp tenderness overlying temporal artery
- sudden, painless loss of vision and/or diplopia due to narrowing of the ophthalmic or posterior ciliary arteries (PCA more common); can affect both eyes
- tongue and jaw claudication (pain in muscles of mastication on prolonged chewing)
- PMR (proximal myalgia, constitutional symptoms, elevated ESR) occurs in 30% of patients
- aortic arch syndrome (involvement of subclavian and brachial branches of aorta resulting in pulseless disease), aortic aneurysm ± rupture are late complications
- constitutional symptoms (e.g. fever of unknown origin in patients ≥65 years) and shoulder/pelvic girdle pain and stiffness

**Medical Emergency**
If untreated, GCA can lead to permanent blindness in 20-25% of patients
Treat on clinical suspicion

### Investigations
- diagnosis made by clinical suspicion, increased ESR, increased CRP, colour doppler U/S of temporal ± axillary arteries (+ halo sign), MRI, consider temporal artery biopsy

### Treatment
- if suspect GCA, immediately start high dose prednisone 1 mg/kg PO in divided doses for 2-4 wk, and then tapering prednisone by 10 mg per 1-2 wk as symptoms resolve; highly effective in treatment and in prevention of blindness and other vascular complications
- consider low dose ASA to help decrease visual loss
- if presenting with vision loss at diagnosis, start methylprednisolone 1000 mg/d IV for 3 d followed by high dose prednisone 1 mg/kg/d PO in divided doses for 4 wk

### Prognosis
- increased risk of thoracic aortic aneurysm and aortic dissection
- yearly CXR ± abdominal U/S as screening

# Seronegative Rheumatic Disease

**Table 25. A Comparison of the Spondyloarthropathies***

| Feature | Ankylosing Spondylitis (AS) | Psoriatic Arthritis (PsA) | Reactive Arthritis (ReA) | Enteropathic Arthritis (EA) |
|---|---|---|---|---|
| M:F | 3:1 | 1:1 | 8:1 | 1:1 |
| Age of Onset | 20s | 35-45 | 20s | Any |
| Peripheral Arthritis | 25% | 96% | 90% | Common |
| Distribution | Axial, LE | Any | LE | LE |
| Sacroiliitis | 100% | 40% | 80% | 20% |
| Dactylitis | Uncommon | Common | Occasional | Uncommon |
| Enthesitis | Common | Common | Common | Less Common |
| Skin Lesions | Rare | 100%<br>Psoriasis eventually<br>70% at onset of arthritis | Occasional<br>Keratoderma<br>blennorrhagica | Occasional<br>Pyoderma, erythema<br>nodosum |
| Uveitis | Common | Occasional | 20% | Rare |
| Urethritis | Rare | Uncommon | Common | Rare |
| HLA-B27 | 90-95% | 40% | 80% | 30% |

LE = lower extremities *Spondylarthropathy: inflammatory joint disease of the vertebral column

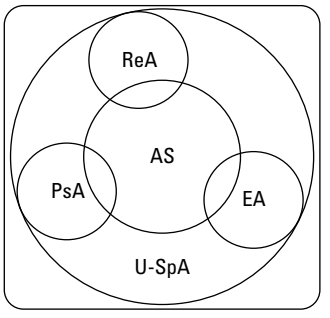



**Figure 10. Spondyloarthropathy subsets**

AS shares some features with the other three types of seronegative spondyloarthopathies such as ReA, EA, PsA and undifferentiated spondyloarthropathy (U-PSA)

Enthesitis: inflammation of tendon or ligament at site of attachment to bone

# Ankylosing Spondylitis

## Definition

- chronic inflammatory arthritis involving the sacroiliac joints and vertebrae
- enthesitis is a major feature (e.g. Achilles tendonitis, plantar fasciitis)
- prototypical spondyloarthropathy

**Table 26. ASAS Classification Criteria for Axial Spondyloarthritis***

| Sacroiliitis on Imaging plus ≥1 AS Feature or HLA-B27 Positive plus ≥2 AS Features | |
|---|---|
| **AS Features** | **Sacroiliitis on Imaging** |
| HLA-B27 positive | Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with AS |
| Inflammatory back pain | OR |
| Arthritis | Definite radiographic sacroiliitis ≥ grade 2 bilaterally or grade 3-4 unilaterally |
| Enthesitis (heel) | |
| Uveitis | |
| Dactylitis | |
| Psoriasis | |
| Crohn's disease/colitis | |
| Good response to NSAIDs | |
| Family history of AS | |
| Elevated CRP | |

*For patients with ≥3 mo back pain and age at onset <45 yr

Consider AS in the differential for causes of aortic regurgitation

**Rule of 2s**
**AS occurs in**
0.2% of the general population
2% of HLA-B27 positive individuals
20% of HLA-B27 positive individuals with affected family member

## Etiology and Pathophysiology

- inflammation → osteopenia → erosion → ossification → osteoproliferation (syndesmophytes)

## Epidemiology

- M:F = 3:1; females have milder disease which may be under-recognized and more peripheral arthritis and upper spine spondylitis
- 90-95% of patients have HLA-B27 (9% HLA-B27 positive in general population)

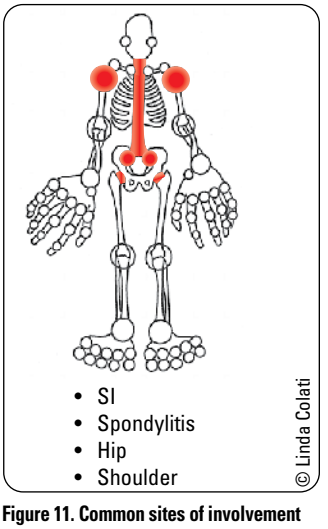



**Figure 11. Common sites of involvement of AS**

**Table 27. Types of Back Pain**

| Parameter | Mechanical | Inflammatory |
|---|---|---|
| **Past History** | ± | ++ |
| **Family History** | – | + |
| **Onset** | Acute | Insidious |
| **Age** | 15-90 yr | <45 yr |
| **Sleep Disturbance** | ± | ++ (worse during 2nd half of night) |
| **Morning Stiffness** | <30 min | >1 h |
| **Involvement of Other Systems** | – | + |
| **Exercise** | Worse | Better |
| **Rest** | Better | Worse |
| **Radiation of Pain** | Anatomic (L5-S1) | Diffuse (thoracic, buttock) |
| **Sensory Symptoms** | + | – |
| **Motor Symptoms** | + | – |

**The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)**
Self-reported scoring system that focuses on fatigue, axial pain, peripheral pain, enthesitis, and morning stiffness

### Signs and Symptoms

- **axial**
  - mid and lower back stiffness, morning stiffness >1 h, night pain, persistent buttock pain, painful sacroiliac joint (+ FABER test)
  - spinal restriction (decreased ROM): lumbar (decreased Schöber), thoracic (decreased chest wall expansion, normal >5 cm at T4), cervical (global decrease, often extension first)
  - postural changes: decreased lumbar lordosis + increased thoracic kyphosis + increased cervical flexion = increased occiput to wall distance (>5 cm)
- **peripheral**
  - asymmetrical large joint arthritis, most often involving lower limb
  - enthesitis: tenderness over tibial tuberosity, or Achilles tendon and plantar fascia insertions into the calcaneus
  - dactylitis: toes or fingers
- **extra-articular manifestations**
  - ophthalmic: acute anterior uveitis is common (25-30% patients)
  - renal: amyloidosis (late and rare), IgA nephropathy
  - gastrointestinal: IBD
  - cardiac: aortitis, aortic regurgitation, pericarditis, conduction disturbances, heart failure (rare)
  - respiratory: apical fibrosis (rare)
  - neurologic: cauda equina syndrome (rare)
  - skin: psoriasis

### Investigations

- x-ray of SI joint: "pseudowidening" of joint due to erosion with joint sclerosis → bony fusion (late), symmetric sacroiliitis
- x-ray of spine: "squaring of edges" from erosion and sclerosis on corners of vertebral bodies (shiny corner sign) leading to ossification of outer fibres of annulus fibrosis (bridging syndesmophytes) → "bamboo spine" radiographically
- MRI of spine: assess activity in early disease; detection of cartilage changes, bone marrow edema, bone erosions, and subchondral bone changes. Best seen on T2 STIR (short tau inversion recovery) images (suppress fat and see bone edema)
- Labs: CBC, elevated ESR/CRP, ALP, $Ca^{2+}$, SPEP, BMD, HLA-B27

### Treatment

- **non-pharmacological therapy**
  - prevent fusion from poor posture and disability through: exercise (e.g. swimming), postural and deep breathing exercises, outpatient PT, smoking cessation
- **pharmacological therapy**
  - NSAIDs (first line of treatment for peripheral and axial disease)
  - glucocorticoids (topical eye drops, local injections, occasionally require systemic steroids prior to other effective Rx)
  - DMARDs only for peripheral arthritis (sulfasalazine, MTX)
  - if inadequate response to two NSAIDs (or DMARD for peripheral arthritis only), consider anti-TNF agents for axial and peripheral involvement
  - manage extra-articular manifestations
- **surgical therapy**
  - hip replacement and vertebral osteotomy for marked deformity (latter done rarely)

### Prognosis

- spontaneous remissions and relapses are common and can occur at any age
- function may be excellent despite spinal deformity
- favourable prognosis if female and age of onset >40 yr
- early onset with hip disease may lead to severe disability; may require arthroplasty

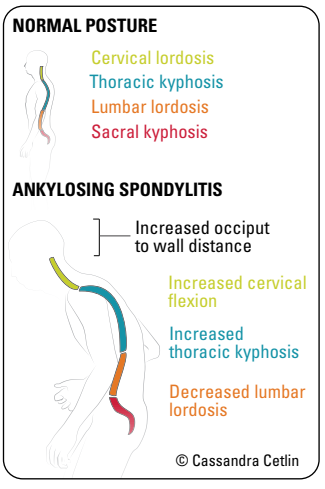



**Figure 12. AS postural change**

**FABER (Flexion, ABduction, and External Rotation) Test**
Passively flex, abduct, then gently externally rotate the leg. If pain is elicited during this movement, the location of the pain may help determine the location of the patient's pathology (e.g. hip joint, sacroiliac joint). However, it is poorly reproducible and inaccurate in discerning inflammatory vs. mechanical back pain

**Modified Schöber Test**
Patient must be standing erect with normal posture
Mark an imaginary line connecting both posterior superior iliac spines (close to the dimples of Venus)
The next mark is placed 10 cm above
The patient bends forward maximally: measure the difference
Report the increase (in cm to the nearest 0.1 cm)
The better of two tries is recorded

**Extra-Articular Manifestations of AS**

**6 As**
**A**tlanto-axial subluxation
**A**nterior uveitis
**A**pical lung fibrosis
**A**ortic incompetence
**A**myloidosis (kidneys)
**A**utoimmune bowel disease (ulcerative colitis)

Both AS and EA feature symmetric sacroiliitis

# Enteropathic Arthritis

- see Gastroenterology, *Inflammatory Bowel Disease*, G22
- MSK manifestations in the setting of either ulcerative colitis or Crohn's disease include peripheral arthritis (large joint, asymmetrical), spondylitis, and hypertrophic osteoarthropathy
- non-arthritic MSK manifestations can occur 2° to steroid treatment of bowel inflammation (arthralgia, myalgia, osteoporosis, AVN)

**Table 28. Comparing Features of Spondylitis vs. Peripheral Arthritis in EA**

| Parameter | Spondylitis | Peripheral Arthritis |
|---|---|---|
| **HLA-B27 Association** | Yes | No |
| **Gender** | M>F | M=F |
| **Onset Before IBD** | Yes | No |
| **Parallels IBD Course** | No | Yes |
| **Type of IBD** | UC=CD | CD |
| **Treatment** | NSAIDs (use cautiously, may exacerbate bowel disease); TNF inhibitors if resistant | NSAIDs, DMARDs; TNF inhibitors if resistant |

# Psoriatic Arthritis

## Definition
- arthritic inflammation associated with psoriasis

## Etiology and Pathophysiology
- unclear but many genetic, immunologic, and some environmental factors involved (e.g. bacterial, viral, and trauma)

## Epidemiology
- psoriasis affects 1% of population
- arthropathy in 15% of patients with psoriasis
- 15-20% of patients will develop joint disease before skin lesions appear

Check "hidden" areas for psoriatic lesions (ears, hair line, umbilicus, gluteal cleft, nails)
TNF-α inhibitors are effective treatments for PsA with no important added risks associated with their short-term use

## Signs and Symptoms
- **dermatologic**
  - well-demarcated erythematous plaques with silvery scale
  - nail involvement: pitting, transverse or longitudinal ridging, discolouration, subungual hyperkeratosis, onycholysis, and oil drops
- **musculoskeletal**
  - 5 general patterns
    - asymmetric oligoarthritis (<5 small and/or large joints affected in asymmetric distribution; most common – 70%)
    - arthritis of DIP joints with nail changes
    - symmetric polyarthritis (similar to RA)
    - sacroiliitis and spondylitis (usually older, male patients)
    - arthritis mutilans (destructive and deforming small joint polyarthritis
  - other findings: dactylitis, enthesopathy, morning stiffness >30 min (50%)
- **ophthalmic**
  - conjunctivitis, iritis (anterior uveitis)
- **cardiac and respiratory** (late findings)
  - aortic insufficiency
  - apical lung fibrosis
- **neurologic**
  - cauda equina syndrome
- **radiologic**
  - floating syndesmophytes
  - pencil-in-cup appearance at IP joints
  - osteolysis, periostitis

## Treatment
- treat skin lesions (e.g. steroid cream, salicylic and/or retinoic acid, tar, UV light)
- NSAIDs or IA steroids (benefit should be seen within a few weeks, should not be the sole therapy >3 mo)
- DMARDs to minimize erosive disease (use early in peripheral joint involvement)
- non-biologic DMARDs (methotrexate, sulfasalazine or leflunomide)
- biologic therapies include anti-TNF agents, anti-IL-17 (secukinumab), and anti-IL-12/23 (ustekinumab)

**Table 29. CASPAR Criteria for PsA***

| Criterion | Description |
|---|---|
| 1. Evidence of psoriasis | Current, past, or family history |
| 2. Psoriatic nail dystrophy | Onycholysis, pitting, hyperkeratosis |
| 3. Negative results for RF | Preferably by ELISA, nephelometry |
| 4. Dactylitis | Current or past history |
| 5. Radiological evidence | Juxta-articular bone formation on hand or foot x-rays |

* To meet the CASPAR (CIASsification criteria for Psoriatic ARthritis) criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥3 points from the above 5 categories
Arthritis Rheum 2006 Aug;54(8):2665-73. Classification criteria for PsA: development

# Reactive Arthritis

## Definition
- one of the seronegative spondyloarthropathies in which patients have a peripheral arthritis (≥1 mo duration) accompanied by one or more extra-articular manifestations that appears shortly after certain infections of the GI or GU tracts
- this term should not be confused with rheumatic fever or viral arthritides

**Clinical Triad of Reactive Arthritis**
- Arthritis
- Conjunctivitis/uveitis
- Urethritis/cervicitis

## Etiology
- onset following an infectious episode either involving the GI or GU tract
  - GI: *Shigella, Salmonella, Campylobacter, Yersinia, C. Difficile* species
  - GU: *Chlamydia* (isolated in 16-44% of ReA cases), *Mycoplasma* species

**"Can't See, Can't Pee, Can't Climb a Tree"**
Triad of conjunctivitis, urethritis, and arthritis is 99% specific (but 51% sensitive) for ReA

- acute clinical course
  - onset 1-4 wk post-infection
  - lasts weeks to months
  - often recurring
  - spinal involvement persists

### Epidemiology
- in HLA-B27 patients, axial > peripheral involvement
- M>F

### Signs and Symptoms
- **musculoskeletal**
  - asymmetric peripheral arthritis, spondylitis/sacroiliitis, enthesitis (Achilles tendinitis, plantar fasciitis), dactylitis
- **ophthalmic**
  - iritis (anterior uveitis), conjunctivitis
- **dermatologic**
  - keratoderma blennorrhagicum (hyperkeratotic skin lesions on palms and soles) and balanitis circinata (small, shallow, painless ulcers of glans penis and urethral meatus) are diagnostic
- **gastrointestinal**
  - oral ulcers, diarrhea
- **genitourinary**
  - urethritis, prostatitis, cervicitis, cystitis, sterile pyuria; presence not related to site of initiating infection

### Investigations
- diagnosis is clinical plus laboratory
- evidence of antecedent or concomitant infection (stool culture, urine, and genital swab testing)
- blood work: normocytic, normochromic anemia, and leukocytosis
- sterile cultures
- serology: HLA-B27 positive, elevated ESR/CRP

### Treatment
- antibiotics for non-articular infections
- NSAIDs (naproxen 500 mg bid/tid, diclofenac 50 mg tid, indomethacin 50 mg tid/qid), physical therapy, exercise
- local therapy
  - IA steroid injection (triamcinolone acetonide)
  - topical steroid for ocular involvement
- systemic therapy
  - corticosteroids (starting dose 20 mg/d)
  - DMARD (for refractory reactive arthritis with peripheral joint involvement only) (sulfasalazine, MTX)
  - TNF-α inhibitors for spinal inflammation (for disease refractory to NSAIDs, DMARD)

### Prognosis
- self-limited, typically 3-5 mo, varies based on pathogen and patient's genetic background
- chronic in 15-20% of cases

# Crystal-Induced Arthropathies

**Table 30. Gout vs. Pseudogout**

| Parameter | Gout | Pseudogout |
|---|---|---|
| **Gender** | M>F | M=F |
| **Age** | Middle-aged males | Usually elderly |
| **Post-menopausal females** | Age >60 yr | |
| **Onset of Disease** | Acute | Acute<br>Chondrocalcinosis is asymptomatic but the clinical feature is generally acute |
| **Crystal Type** | Monosodium urate<br>Negative birefringence (yellow when parallel to compensator filter), needle-shaped | CPPD<br>Positive birefringence (blue when parallel), rhomboid-shaped |
| **Distribution** | First MTP classically; also midfoot, ankle, knee, or polyarticular | Knee, wrist; monoarticular, or polyarticular if chronic |
| **Radiology (note findings are non-specific)** | Erosions | Chondrocalcinosis<br>OA (knee, wrist, 2nd and 3rd MCP) |
| **Treatment** | Acute: NSAIDs, corticosteroids, colchicine<br>Chronic: ± allopurinol, fuboxostat | NSAIDs, corticosteroids |

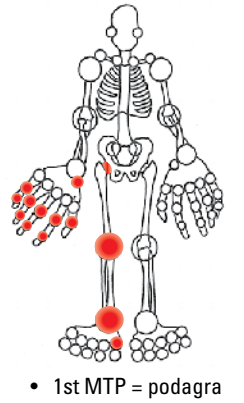



**Figure 13. Common sites of involvement of gout** (asymmetric joint involvement)

# Gout

## Definition
- derangement in purine metabolism resulting in hyperuricemia; monosodium urate crystal deposits in tissues (tophi) and synovium (microtophi)

## Etiology and Pathophysiology
- uric acid can be obtained from the diet or made endogenously by xanthine oxidase, which converts xanthine to uric acid
- an excess of uric acid results in hyperuricemia
- uric acid can deposit in the skin/subcutaneous tissues (tophi), synovium (micro-tophi) and kidney, where they can crystalize to form monosodium urate crystals that lead to gout
- non-modifiable risk factors include: genetic mutations, male gender, and advanced age
- modifiable risk factors include: diet (alcohol, purine rich foods such as meats and seafoods, fructose/sugar sweetened foods; see list of precipitants below)
- other risk factors: renal failure, metabolic syndrome, dehydration (e.g. diuretics)

## Signs and Symptoms
- single episode progressing to recurrent episodes of acute inflammatory arthritis
- **acute gouty arthritis**
  - severe pain, redness, joint swelling, usually involving lower extremities
  - joint mobility may be limited
  - attack will subside spontaneously within days to weeks (5-10 d); may recur
- **tophi**
  - urate deposits on cartilage, tendons, bursae, soft tissues, and synovial membranes
  - common sites: first MTP, ear helix, olecranon bursae, tendon insertions (common in Achilles tendon)
- **kidney**
  - gouty nephropathy
  - uric acid nephrolithiasis

## Investigations
- joint aspirate: >90% of joint aspirates show crystals of monosodium urate (negatively birefringent, needle-shaped) if done early in course of presentation
- x-rays may show tophi as soft tissue swelling, bone/joints - punched-out lesions, erosion with "over-hanging" edge
- correlated with hyperuricemia in the blood
- may see elevated WBC and ESR (nonspecific)

## Treatment
- **acute gout**
  - NSAIDs: high dose, then taper as symptoms improve
  - corticosteroids: IA, oral, or intra-muscular (if renal, cardiovascular or GI disease and/or if NSAIDs contraindicated or failed)
  - colchicine 1.2 mg at the first signs of an attack followed by 0.6 mg one hour later and 0.6 mg bid on subsequent days until the attack has resolved
  - allopurinol can worsen an acute attack (do not start during acute flare)
- **chronic gout**
  - conservative
    - avoid foods with high purine content (e.g. visceral meats, sardines, shellfish, beans, peas)
    - avoid drugs with hyperuricemic effects (e.g. pyrazinamide, ethambutol, thiazide, alcohol)
  - medical
    - anti-hyperuricemic drugs (allopurinol and febuxostat): decrease uric acid production by inhibiting xanthine oxidase
    - uricosuric drugs (probenecid, sulfinpyrazone): very rarely used in combination with allopurinol or febuxostat in patients in whom hyperuricemia is not controlled with the latter
  - prophylaxis with low dose NSAID/colchicine may be required prior to starting antihyperuricemic drugs
  - in renal disease secondary to hyperuricemia, use low-dose allopurinol and monitor Cr
- indications for treatment with antihyperuricemic medications include
  - recurrent attacks (more than 2-3 yr), tophi, bone erosions, urate kidney stones
  - perhaps in renal dysfunction with very high urate load (controversial)





An acute gout attack may mimic cellulitis; however, joint mobility is usually preserved in cellulitis unless it overlaps a joint



**Precipitants of Gout**

**Drugs are FACT**
**F**urosemide
**A**spirin® (low dose)/**A**lcohol
**C**yclosporine
**T**hiazide diuretics

**Foods are SALT**
**S**eafood
**A**lcohol (beer and spirits)
**L**iver and kidney
**T**urkey (meat)



The majority of people with hyperuricemia do not have gout
Normal or low uric acid levels do not rule out gout



**10 Recommendations on the Diagnosis and Management of Gout**
Ann of Rheum Dis 2013;73:328-335

1. Identification of monosodium urate crystals in joint aspirate should be performed for a definitive diagnosis of gout.
2. Gout/hyperuricemia should prompt investigations of renal function and CV risk factors.
3. Acute gout should be treated with colchicine, NSAIDs, and/or glucocorticoids.
4. Patients should be counselled about lifestyle.
5. Allopurinol is first line for urate lowering therapy, with uricosurics as second line.
6. Patients should be informed about the risk of acute gout flare with initiation of urate lowering therapy; colchicine prophylaxis should be considered.
7. Allopurinol can be used in patients with mild /moderate renal impairment with slow titration and monitoring.
8. Treatment goal is urate <0.36 mM and absence of attacks and resolution of tophi.
9. Tophi should be treated medically by lowering serum urate to <0.3 mM. Surgery is only for select cases.
10. Prophylactic pharmacological management of asymptomatic hyperuricemia is not recommended.

## Pseudogout (Calcium Pyrophosphate Dihydrate Disease)

### Definition
- joint inflammation caused by calcium pyrophosphate crystals

### Etiology and Pathophysiology
- acute inflammatory arthritis due to phagocytosis of IgG-coated CPPD crystals by neutrophils and subsequent release of inflammatory mediators within joint space
- Usually monoarticular but can be polyarticular
- slower in onset in comparison to gout, lasts up to 2-3 wk but is self-limited

### Risk Factors
- old age, advanced OA, neuropathic joints
- other associated conditions: hyperparathyroidism, hypothyroidism, hypomagnesemia, hypophosphatasia (low ALP), DM, hemochromatosis

### Signs and Symptoms
- affects knees, wrists, MCPs, hips, shoulders, elbows, ankles, big toe, spine
- asymptomatic crystal deposition (seen on radiograph only)
- acute crystal arthritis (self-limited flares of acute inflammatory arthritis resembling gout)
- pseudo-OA (progressive joint degeneration, sometimes with episodes of acute inflammatory arthritis)
- pseudo-RA (symmetrical polyarticular pattern with morning stiffness and constitutional symptoms)
- frequently triggered by dehydration, acute illness, surgery, trauma

### Investigations
- must aspirate joint to rule out septic arthritis, gout
- CPPD crystals: present in 60% of patients, often only a few crystals, positive birefringence (blue) and rhomboid shaped
- x-rays show chondrocalcinosis in 75%: radiodensities in fibrocartilaginous structures (e.g. knee menisci) or linear radiodensities in hyaline articular cartilage

### Treatment
- joint aspiration, rest, and protection
- NSAIDs: also used for maintenance therapy
- prophylactic colchicine 0.6-1.2 mg/d PO (controversial)
- IA or oral steroids to relieve inflammation

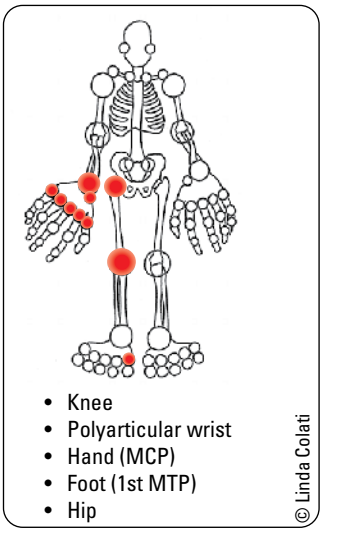



**Figure 14. Common sites of involvement of CPPD**

# Non-Articular Rheumatism

### Definition
- disorders that primarily affect soft tissues or periarticular structures
- includes bursitis, tendinitis, tenosynovitis, fibromyalgia, and PMR

## Polymyalgia Rheumatica

### Definition
- characterized by pain and stiffness of the proximal extremities (girdle area)
- closely related to GCA (15% of patients with PMR develop GCA)
- no muscle weakness

**Table 31. PMR Classification Criteria Scoring Algorithm***

| | Points without U/S (0-6) | Points with Abnormal U/S** (0-8) |
|---|---|---|
| Morning stiffness duration >45 min | 2 | 2 |
| Hip pain or limited ROM | 1 | 1 |
| Absence of RF or ACPA | 2 | 2 |
| Absence of other joint involvement | 1 | 1 |
| At least one shoulder with subdeltoid and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least one hip with synovitis and/or trochanteric bursitis on U/S | N/A | 1 |
| Both shoulders with subdeltoid bursitis, biceps tenosynovitis, or gleno-humeral synovitis on U/S | N/A | 1 |

*Required criteria: age ≥50 yr, bilateral shoulder aching, and abnormal ESR/CRP
**A score of 4 or more is categorized as PMR in the algorithm without U/S and a score of 5 or more is categorized as PMR in the algorithm with U/S
**Optional U/S criteria
Ann Rheum Dis 2012;71:484-492

### Epidemiology
- incidence 50 per 100,000 per year in those >50 yr
- age of onset typically >50 yr, F:M = 2:1

### Signs and Symptoms
- constitutional symptoms prominent (fever, weight loss, malaise)
- pain and stiffness of symmetrical proximal muscles (neck, shoulder and hip girdles, thighs)
- gel phenomenon (stiffness after prolonged inactivity)
- physical exam reveals tender muscles, but no true weakness or atrophy

### Investigations
- blood work: often shows anemia of chronic disease, elevated platelets, elevated ESR and CRP, and normal CK; up to 5% of PMR reported with normal inflammatory markers

### Treatment
- goal of therapy: symptom relief
- start with prednisone dose of 15-20 mg PO OD, reconsider diagnosis if no response within several days
- taper slowly over 1 yr period with closely monitoring
- relapses should be diagnosed and treated on clinical basis; do not treat a rise in ESR as a relapse
- treat relapses aggressively (50% relapse rate)
- monitor for steroid side effects, glucocorticoid-induced osteoporosis prevention, and follow for symptoms of GCA

## Fibromyalgia

### Definition
- chronic (>3 mo), widespread (axial, left- and right-sided, upper and lower segment), non-articular pain with characteristic tender points

### Diagnosis

**Table 32. 2010 ACR Preliminary Diagnostic Criteria for Fibromyalgia**

| Criteria | Comments |
|---|---|
| Widespread Pain Index = number of areas in which the patient had pain over the last week (max score = 19):<br>L and R: shoulder girdle, upper arm, lower arm, hip, upper leg, lower leg, jaw<br>One Area: chest, abdomen, upper back, lower back, neck<br><br>Symptom Severity Score = sum of:<br>a) severity of fatigue<br>b) waking unrefreshed<br>c) cognitive symptoms over the past week<br>d) extent of somatic symptoms (IBS, H/A, abdominal pain/ cramps, dry mouth, fever, hives, ringing in ears, vomiting, heartburn, dry eyes, SOB, loss of appetite, rash, hair loss, easy bruising, etc.)<br>all (a-d) rated on 0-3 scale: 0 = no problem, 1 = mild, 2 = moderate, 3 = severe | A patient satisfies diagnostic criteria for fibromyalgia if the following 3 conditions are met:<br>1. Widespread Pain Index (WPI) ≥7 and Symptom Severity (SS) scale score ≥5 or WPI 3–6 and SS scale score ≥9<br>2. Symptoms have been present at a similar level for at least 3 mo<br>3. The patient does not have a disorder that would otherwise explain the pain |

Arthritis Care and Research 2010;62(5):600-610

### Epidemiology
- F:M = 3:1
- primarily ages 25-45 yr, some adolescents
- prevalence of 2-5% in general population
- overlaps with chronic fatigue syndrome and myofascial pain syndrome
- strong association with psychiatric illness

### Signs and Symptoms
- widespread aching, stiffness
- easy fatigability
- sleep disturbance: non-restorative sleep, difficulty falling asleep, and frequent wakening
- symptoms aggravated by physical activity, poor sleep, emotional stress
- patient feels that joints are diffusely swollen although joint examination is normal
- neurologic symptoms of hyperalgesia, paresthesias, allodynia
- associated with irritable bowel or bladder syndrome, migraines, tension H/As, restless leg syndrome, obesity, depression, and anxiety
- physical exam should reveal only tenderness with palpation of soft tissues, with no specificity for trigger/tender points

### Investigations
- blood work: includes TSH and ESR; all typically normal unless unrelated, underlying illness present
- serology: do not order ANA or RF unless there is clinical suspicion for a connective tissue disease
- laboratory sleep assessment

### Treatment

- **non-pharmacological therapy**
  - education
  - exercise program (walking, aquatic exercises), physical therapy (good posture, stretching, muscle strengthening, massage)
  - stress reduction, CBT
  - no evidence for alternative medicine such as biofeedback, meditation, acupuncture
- **pharmacological therapy**
  - low dose tricyclic antidepressant (e.g. amitriptyline)
    - for sleep restoration
    - select those with lower anticholinergic side effects
  - SNRI: duloxetine, milnacipran
  - anticonvulsant: pregabalin, gabapentin
  - analgesics may be beneficial for pain that interferes with sleep (NSAIDs, not narcotics)

### Prognosis

- variable; usually chronic, unless diagnosed and treated early

**Table 33. Clinical Features of Inflammatory Myopathy vs. Polymyalgia Rheumatica vs. Fibromyalgia**

| | Polymyositis | PMR | Fibromyalgia |
|---|---|---|---|
| **Epidemiology** | F > M, 40-50 yr | F > M, >50 yr | F > M, 25-45 yr |
| **Muscle Involvement** | Proximal muscle | Proximal muscle | Diffuse |
| **Weakness** | Yes | No | No |
| **Pain** | Painless | Painful | Painful |
| **Stiffness** | Mild | Significant morning and gelling stiffness (shoulders, neck, hips) | May have morning stiffness |
| **Investigations** | Muscle biopsy, CK, EMG, R/O malignancy | ESR/CRP, R/O giant cell arteritis | Sleep assessment, TSH |
| **ESR/CRP** | Usually normal | Markedly elevated | Normal |
| **Treatment** | High dose steroids, immunosuppressants | Low dose steroids | Exercise, TCAs, SNRIs, anticonvulsants |

# Common Medications

**Table 34. Common Medications for Osteoarthritis**

| Class | Generic Drug Name | Trade Name | Dosing (PO) | Indications | Contraindications | Adverse Effects |
|---|---|---|---|---|---|---|
| Analgesic | acetaminophen | Tylenol® | 500 mg tid q4h<br>(3 g daily max) | 1st line | | Hepatotoxicity<br>Overdose<br>Potentiates warfarin |
| NSAIDs | ibuprofen<br>diclofenac<br>diclofenac/misoprostol<br>naproxen<br>meloxicam | Voltaren®<br>Arthrotec®<br>Naprosyn®<br>Aleve®<br>Mobicox® | 200-600 mg tid<br>25-50 mg tid<br>50-75/200 mg tid<br>125-500 mg bid<br>7.5-15 mg OD | 2nd line | GI bleed<br>Renal impairment<br>Allergy to ASA, NSAIDs<br>Pregnancy (T3) | Nausea, tinnitus, vertigo, rash, dyspepsia, GI bleed, PUD, hepatitis, renal failure, HTN, nephrotic syndrome |
| **COX-2 INHIBITORS** | | | | | | |
| | celecoxib | Celebrex® | 200 mg OD | High risk for GI bleed:<br>age >65<br>Hx of GI bleed, PUD | Renal impairment<br>Cardiovascular disease | Delayed ulcer healing<br>Renal/hepatic impairment<br>Rash |

| Other Treatments | Comments |
|---|---|
| Combination analgesics (acetaminophen + codeine, acetaminophen + NSAIDs) | Enhanced short-term effect compared to acetaminophen alone<br>More adverse effects: sedation, constipation, nausea, GI upset |
| IA corticosteroid injection | Short-term (weeks-months), joint specific treatment<br>Decrease in pain and improvement in function<br>Used for management of an IA inflammatory process when infection has been ruled out |
| IA hyaluronic acid q6mo | Used for mild-moderate OA of the knees, however little supporting evidence, and not considered to be effective<br>Precaution with chicken/egg allergy |
| Topical NSAIDs | % wt/wt topical diclofenac (Pennsaid®, Voltaren Emulgel®)<br>May use for patients who fail acetaminophen treatment and who wish to avoid systemic therapy, better on small joints |
| Capsaicin cream | Mild decrease in pain |
| Glucosamine sulfate ± chondroitin | Limited clinical studies. No regulation by Health Canada |

**Table 35. Disease Modifying Anti-Rheumatic Drugs (DMARDs)**

| Generic Drug Name | Trade Name | Dosing | Contraindications | Adverse Effects |
|---|---|---|---|---|
| **COMMONLY USED** | | | | |
| hydroxychloroquine $ | Plaquenil® | 400 mg PO OD initially 200-400 mg PO OD maintenance (6.5 mg/kg ideal body weight per day to a maximum of 400 mg/d) | Retinal disease, G6PD deficiency | GI symptoms, skin rash, macular damage, neuromyopathy Requires regular ophthalmological screening to monitor for retinopathy |
| sulfasalazine $ | Salazopyrim® Azulfidine® (US) | 1000 mg PO bid-tid | Sulfa/ASA allergy, kidney disease, G6PD deficiency | GI symptoms, rash, H/A, leukopenia |
| methotrexate $ | Rheumatrex® Folex/Mexate® | 7.5-25 mg PO/IM/SC qweekly | Bone marrow suppression, liver disease, significant lung disease, immunodeficiency, pregnancy, EtOH abuse | Oral ulcers, GI symptoms, cirrhosis, myelosuppression, pneumonitis, tubular necrosis |
| leflunomide $$ | Arava® | 10-20 mg PO OD | Liver disease, lung disease | Alopecia, GI symptoms, liver dysfunction, pulmonary infiltrates |
| **NOT COMMONLY USED** | | | | |
| cyclosporine $$ | Neoral® | 2.5-3 mg/kg/d divided and given in 2 doses PO | Kidney/liver disease, infection, HTN | HTN, decreased renal function, hair growth, tremors, bleeding |
| gold (injectable) $ | Solganal® Myocrysine® | 50 mg IM q1wk after gradual introduction | IBD, kidney/liver disease | Rash, mouth soreness/ulcers, proteinuria, marrow suppression |
| azathioprine $ | Imuran® | 2/5 mg/kg/d PO once daily | Kidney/liver disease TPMT deficiency | Rash, pancytopenia (especially ↓ WBC, ↑ AST, ALT), biliary stasis, vomiting, diarrhea |
| cyclophosphamide $ | Cytoxan® | 1 g/m²/mo IV as per protocol | Kidney/liver disease | Cardiotoxicity, GI symptoms, hemorrhagic cystitis, nephrotoxicity, bone marrow suppression, sterility |

| Generic Drug Name | Trade Name | Dosing | Mechanism of Action |
|---|---|---|---|
| **NEWER DMARDs (Biologics)** | | | |
| etanercept $$$ | Enbrel® | 25 mg biweekly or 50 mg weekly SC | Fusion protein of TNF receptor and Fc portion of IgG |
| infliximab $$$ | Remicade® | 3-5 mg/kg IV q8wk | Chimeric mouse/human monoclonal anti-TNF |
| adalimumab $$$ | Humira® | 40 mg SC q2wk | Monoclonal anti-TNF |
| golimumab $$$ | Simponi® | 50 mg SC q1mo | Monoclonal anti-TNF |
| certolizumab $$$ | Cimzia® | 400 mg SC q2wk x3 then 200 mg SC q4wk | PEGylated monoclonal anti-TNF |
| apremilast $$$ | Otezla® | Day 1: 10 mg (AM), titrate up to 30 mg BID by day 6 | Inhibitor of PDE4 which inhibits production of TNFα |
| abatacept $$$ | Orencia® | IV infusion | Costimulation modulator of T cell activation |
| rituximab $$$ | Rituxan® | 2 IV infusions, 2 wk apart | Causes B-cell depletion, binds to CD20 |
| tocilizumab $$$ | Actemra® | 4-8 mg/kg IV q4wk | Interleukin-6 receptor antagonist |
| tofacitinib $$ | Xeljanz® | 5 mg BID | Inhibits the JAK enzyme and thus interferes with JAK-STAT signaling pathway |



**Risks of Biologics**
Patients require negative TB skin test, chest x-ray, and negative hepatitis B virus serology prior to starting any of these medications. Increased risk of: serious infections, worsening heart failure, multiple sclerosis, and positive auto-antibodies

# Landmark Rheumatology Trials

| Trial | Reference | Results |
|---|---|---|
| **RHEUMATOID ARTHRITIS** | | |
| ATTEST | Ann Rheum Dis 2008;67:1096-103 | Abatacept and infliximab have similar efficacy in RA patients who have failed MTX |
| ATTRACT | Lancet 1999;354:1932-9 | Infliximab and MTX combined are more effective than MTX alone for patients with active RA |
| COMET | Lancet 2008;372:375-82 | Etanercept add-on therapy increases rates of remission in early RA |
| ERA | NEJM 2000;343:1586-93 | Etanercept more rapidly decreases symptoms in early RA compared to MTX |
| European Leflunomide Study Group | Lancet 1999;353:259-66 | Leflunomide is equal in efficacy to sulphasalazine and superior to placebo |
| FIN-RACo | Lancet 1999;353:1568-73 | Combination therapy with DMARDs improves remission rates in early RA |
| Infliximab and MTX | NEJM 2000;343:1594-602 | Infliximab combined with MTX reduces joint damage in RA |
| Leflunomide Rheumatoid Arthritis Investigators Group | Arch Intern Med 1999;159:2542-50 | Leflunomide is equivalent to MTX therapy and superior to placebo |
| PREMIER | Arthritis Rheum 2006;54:26-37 | Combination therapy with adalimumab and MTX is superior to either treatment alone, in patients with early RA |
| Swefot | Lancet 2009;374:459-66 | Anti-TNF agents are more effective second-line therapy than DMARDs in patients who fail MTX |
| **OSTEOARTHRITIS** | | |
| GAIT | NEJM 2006;354:795-808 | Glucosamine, chondroitin, and the combination of both are no more effective than placebo in treatment of knee OA |
| Hyaluronan | Ann Rheum Dis 2010;69:1097-102 | Hyaluronan injections do not improve disease activity in patients with moderate-severe knee OA |
| **SLE** | | |
| Belimumab | Lancet 2011;377:721-31 | Treatment with belimumab reduces the incidence of BILAG A and B flares in patients with SLE compared to placebo |
| BILAG open-RCT | Rheumatology 2010;49:723-32 | Low dose cyclosporine and azathioprine are equivalent in efficacy as maintenance therapy for SLE |
| Mycophenylate mofetil or intravenous cyclophosphamide | NEJM 2005;353:2219-28 | Mycophenylate mofetil is more efficacious than cyclophosphamide in inducing remission of SLE nephritis |
| **CONNECTIVE TISSUE DISEASES** | | |
| Azathioprine or MTX maintenance for ANCA-associated vasculitis | NEJM 2008;359:2790-803 | MTX and azathioprine are equally safe and effective as maintenance agents in ANCA vasculitis |
| CYCLOPS | Ann Intern Med 2009;69:670-80 | Pulse cyclophosphamide therapy requires a lower cumulative dose compared to daily oral treatment in ANCA vasculitis |
| Cyclophosphamide in scleroderma lung disease | NEJM 2006;354:2655-66 | Cyclophosphamide therapy leads to transient improvements in lung function, skin scores, and overall health in patients with scleroderma |
| Etanercept plus standard therapy for granulomatosis with polyangiitis | NEJM 2005;352:351-61 | Etanercept is not effective in inducing remission in patients with ANCA vasculitis |
| Mycophenylate mofetil vs. azathioprine for maintenance in ANCA-associated vasculitis | JAMA 2010;304:2381-8 | Mycophenylate mofetil is less effective than azathioprine for maintaining disease remission in ANCA-associated vasculitis |
| Rituximab versus cyclophosphamide for ANCA-associated vasculitis | NEJM 2010;363:221-32 | Rituximab is not inferior to cyclophosphamide for induction of remission in ANCA vasculitis |
| **GOUT** | | |
| Febuxostat vs. allopurinol | NEJM 2005;353:2450-61 | Febuxostat is more effective than allopurinol at lowering serum urate, and has similar effectiveness on flare reduction |
| **ANKYLOSING SPONDYLITIS** | | |
| Adalimumab | Arthritis Rheum 2006;54:2136-46 | Adalimumab induced partial remission in 22% of AS patients |
| ASSERT (rituximab) | Arthritis Rheum 2005;52:582-91 | Sixty percent of patients treated with rituximab had a clinical response to the medication |
| ATLAS (adalimumab) | J Rheumatol 2008;35:1346-53 | Compared to placebo, adalimumab significantly reduces pain and fatigue in AS patients |
| Infliximab in AS | Lancet 2002;359:1187-93 | Infliximab induces regression of symptoms in 50% of patients and is superior to placebo |
| SPINE (etanercept) | Ann Rheum Dis 2011;70:799-804 | Etanercept has short-term efficacy for patients with advanced AS and reduces disease severity |
| Sulfasalazine | Arthritis Rheum 1995;38:618-27 | Sulfasalazine is superior to placebo in treatment of patients with seronegative spondyloarthropathy |

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# Urology

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# Acronyms

| | |
|---|---|
| β-hCG | beta-human chorionic gonadotropin |
| ABx | antibiotics |
| AFP | alpha-fetoprotein |
| ART | assisted reproductive technologies |
| AUA | American Urological Association |
| BCG | Bacillus Calmette-Guérin |
| BPH | benign prostatic hyperplasia |
| BPKVP | bipolar plasma kinetic vaporization of the prostate |
| CAH | congenital adrenal hyperplasia |
| CaP | cancer of the prostate |
| CBI | continuous bladder irrigation |
| CFU | colony-forming unit |
| CHF | congestive heart failure |
| CIC | clean intermittent catheterization |
| CIS | carcinoma in situ |
| CMG | cystometrogram |
| CPPS | chronic pelvic pain syndrome |
| CTU | CT urography |
| CUA | Canadian Urological Association |
| CVA | costovertebral angle |
| d/c | discharge |
| DHT | dihydrotestosterone |
| DMSA | dimercaptosuccinic acid |
| DRE | digital rectal exam |
| DSD | detrusor sphincter dyssynergia |
| EBRT | external beam radiation therapy |
| ED | erectile dysfunction |
| EPS | expressed prostatic secretions |
| ESWL | extracorporeal shockwave lithotripsy |
| FNA | fine needle aspiration |
| GA | general anesthesia |
| GAG | glycosaminoglycan |
| HIFU | high-intensity focused ultrasound |
| HPF | high power field |
| HPTA | hypothalamic-pituitary-testicular axis |
| ICSI | intracytoplasmic sperm injection |
| IFN-α | interferon-alpha |
| IL-2 | interleukin-2 |
| IPSS | International Prostate Symptom Score |
| ISD | intrinsic sphincter deficiency |
| IUI | intrauterine insemination |
| IVF | in vitro fertilization |
| IVP | intravenous pyelogram |
| KUB | kidneys, ureters, bladder |
| LFT | liver function test |
| LMN | lower motor neuron |
| LUTS | lower urinary tract symptoms |
| MAG3 | mercaptoacetyltriglycine |
| MET | medical expulsive therapy |
| MS | multiple sclerosis |
| NSGCT | non-seminomatous germ cell tumour |
| OPQRSTU | onset, position, quality, radiation, severity, temporality, deja vu |
| PCKD | polycystic kidney disease |
| PCNL | percutaneous nephrolithotomy |
| PDE | phosphodiesterase |
| PID | pelvic inflammatory disease |
| PMC | pontine micturition centre |
| POD | post-obstructive diuresis |
| PSA | prostate specific antigen |
| PUV | posterior urethral valve |
| PVD | peripheral vascular disease |
| PVR | post-void residual |
| QOL | quality of life |
| RCC | renal cell carcinoma |
| RFA | radio-frequency ablation |
| RP | radical prostatectomy |
| RPLND | retroperitoneal lymph node dissection |
| RTA | renal tubular acidosis |
| RUG | retrograde urethrogram |
| SA | semen analysis |
| SCC | squamous cell carcinoma |
| SLN | sentinel lymph node |
| SUI | stress urinary incontinence |
| TMP/SMX | trimethoprim/sulfamethoxazole |
| TRUS | transrectal ultrasound |
| TUIP | transurethral incision of the prostate |
| TUNA | transurethral needle ablation |
| TURBT | transurethral resection of bladder tumour |
| TURP | transurethral resection of the prostate |
| U/A | urinalysis |
| U/O | urine output |
| U/S | ultrasound |
| UC | urothelial carcinoma |
| UMN | upper motor neuron |
| UPJ | ureteropelvic junction |
| URS | ureterorenoscopy |
| UTI | urinary tract infection |
| UVJ | ureterovesicular junction |
| VB1 | voided bladder, initial (urethra) |
| VB2 | voided bladder, midstream (bladder) |
| VB3 | voided bladder, post-massage/digital rectal exam |
| VCUG | voiding cystourethrogram |
| VIU | visual internal urethrotomy |
| VUR | vesicoureteral reflux |

# Basic Anatomy Review

- recall that the anatomical position of the penis is erect; therefore, the anatomical ventral side of the penis appears to be the dorsal side of the flaccid penis

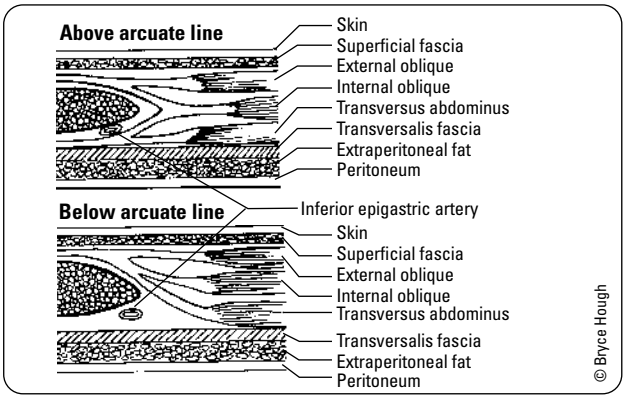



**Figure 1. Midline cross-section of abdominal wall**

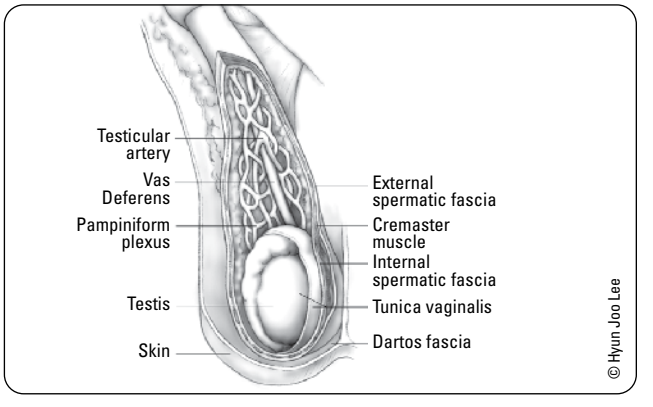



**Figure 2. Anatomy of scrotum**

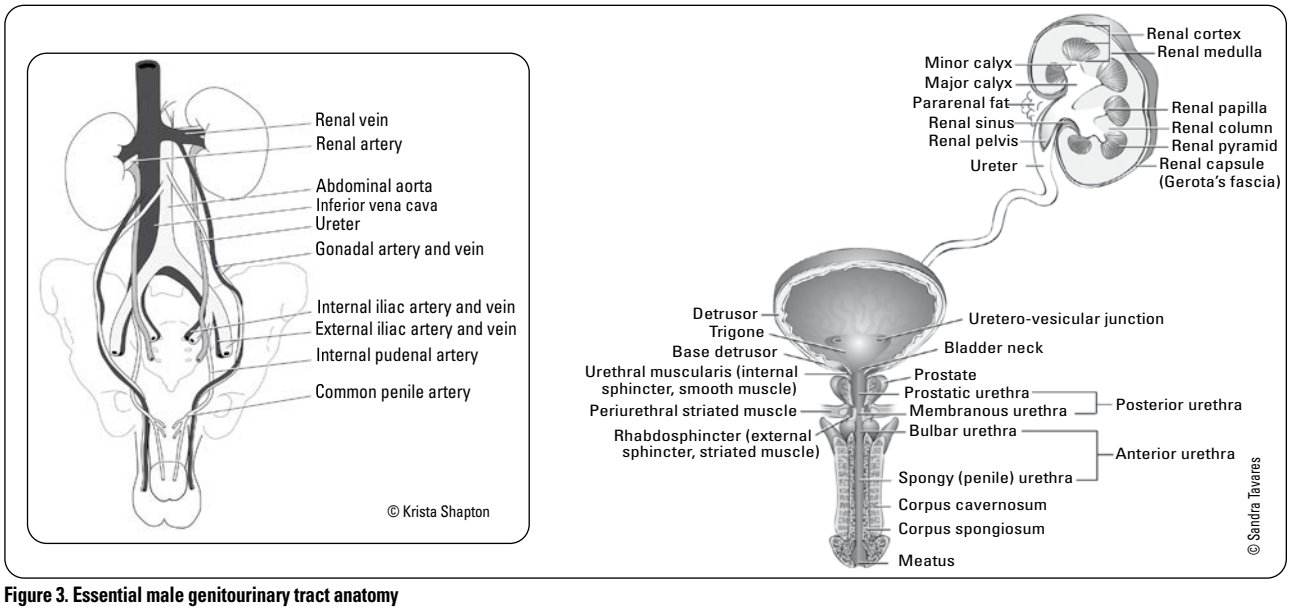



**Figure 3. Essential male genitourinary tract anatomy**

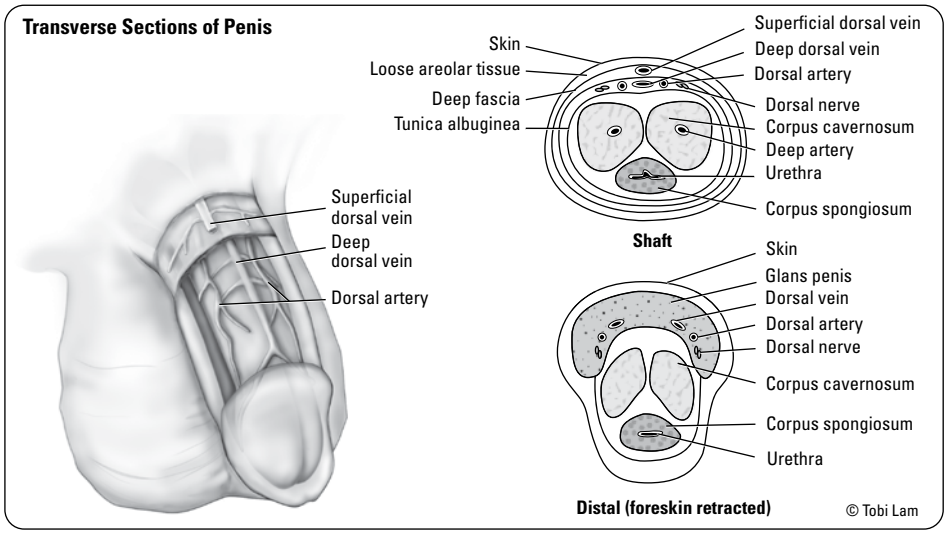



**Figure 4. Cross section of the penis**

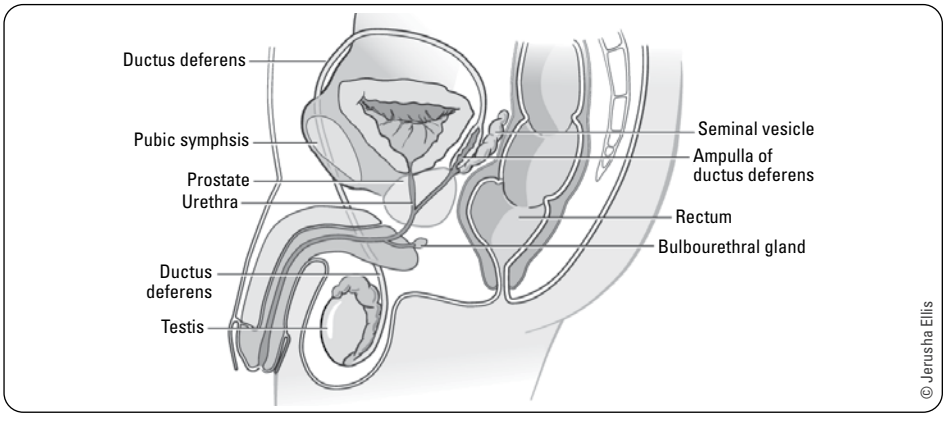



**Figure 5. Median sagittal section of the male pelvis and perineum**

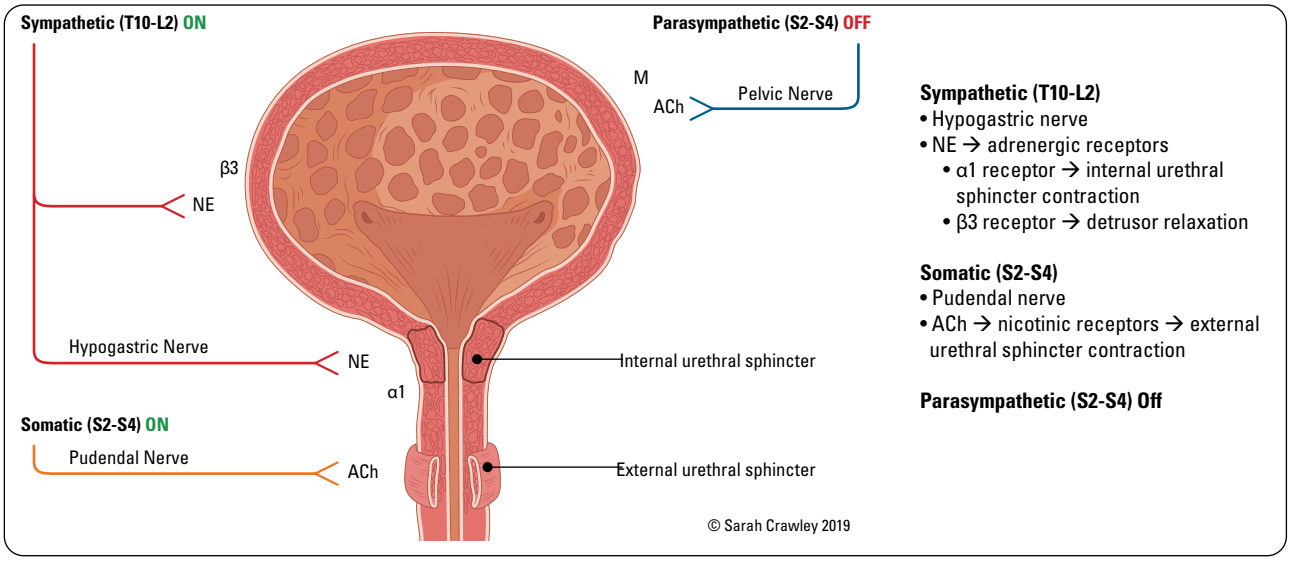



**Figure 6. Bladder innervation during storage phase**

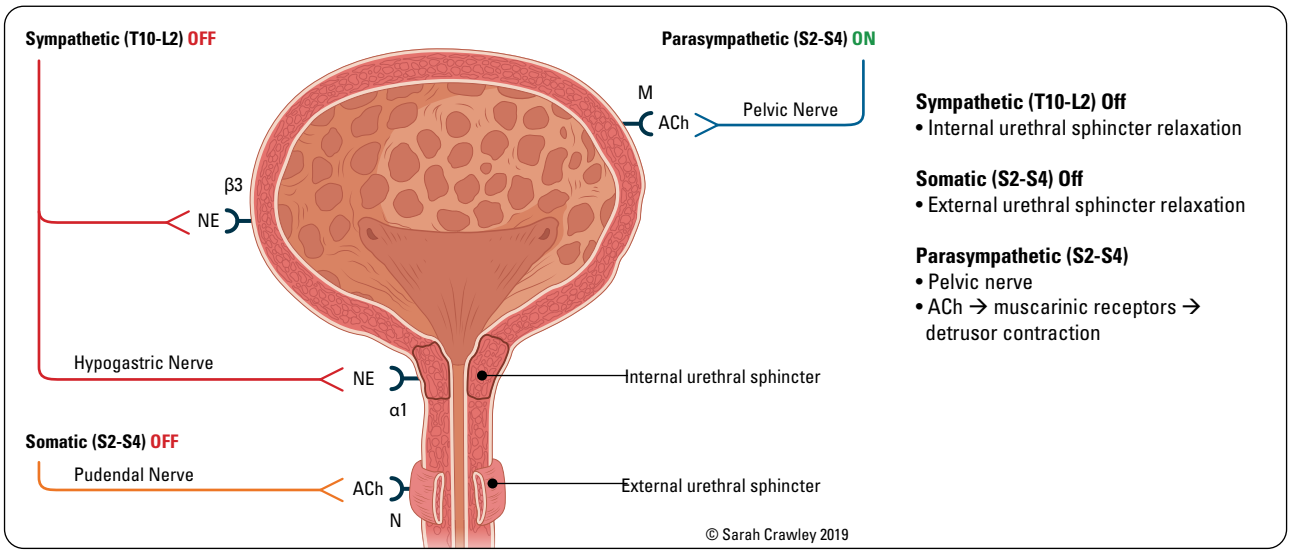



**Figure 7. Bladder innervation during voiding phase**

# Urologic History

- follow OPQRSTU approach
  - note that pain may not be limited to the genital region (e.g. lower abdomen, CVA)
- urinary habits
  - LUTS (see *Lower Urinary Tract Symptoms*, U7)
  - storage symptoms (FUN): frequency, urgency (rush to toilet), nocturia
  - voiding symptoms (SHED): stream changes/straining, hesitancy, incomplete emptying, post-void dribbling
  - dysuria: burning, pain on voiding
  - hematuria: blood clots, red/pink tinged urine (see *Hematuria*)
  - incontinence: stress, urgency, mixed, overflow (see *Incontinence,* U6)
- sexual function
  - scrotal mass (see *Scrotal Mass*, U31)
  - ED (see *Erectile Dysfunction*, U33)
  - infertility (see *Infertility*, U36)
- associated symptoms
  - N/V
  - bowel dysfunction
- constitutional symptoms
  - fever, chills, unintentional weight loss, night sweats, fatigue, malaise, bone pain
- risk factors: past urologic disease (e.g. UTI, stones, STI, cancers, anatomic abnormalities), family Hx, medications, lifestyle factors (smoking, alcohol, inactivity), trauma, previous surgical procedures

Always ask about sexual function on history. Change in erectile function can be one of the first symptoms that there is concomitant vascular disease. If there is new onset ED, consider screening for DM and CAD risk factors

# Hematuria

## Macroscopic (Gross) Hematuria

### Definition
- blood in the urine that can be seen with the naked eye

### Classification
- see Nephrology, NP21

### Etiology

**Table 1. Etiology by Age Group**

| Age (yr) | Etiology | |
|---|---|---|
| 0-20 | UTI, glomerulonephritis, congenital abnormalities | |
| 20-40 | UTI, stones, bladder tumour, exercise | |
| 40-60 | Male: bladder tumour, stones, UTI | Female: UTI, stones, bladder tumour |
| >60 | Male: BPH, bladder tumour, UTI, RCC | Female: bladder tumour, UTI, RCC |

Gross, painless hematuria in adults is bladder cancer until proven otherwise

**Table 2. Etiology by Type**

| Pseudohematuria | Infectious/ Inflammatory | Malignancy | Benign | Structural | Hematologic |
|---|---|---|---|---|---|
| Vaginal bleeding<br>Dyes (beets, rhodamine B in candy and juices)<br>Hemoglobin (hemolytic anemia)<br>Myoglobin (rhabdomyolysis)<br>Drugs (rifampin, phenazopyridine, phenytoin)<br>Porphyria<br>Laxatives (phenolphthalein) | Pyelonephritis<br>Cystitis<br>Urethritis<br>Glomerulonephritis<br>Interstitial nephritis<br>Tuberculosis | RCC (mainly adults)<br>Urothelial cancer<br>Wilms' tumour (mainly pediatric)<br>Prostate cancer<br>Leukemia | BPH<br>Polyps<br>Exercise-induced | Stones<br>Trauma<br>Foreign body<br>Urethral stricture<br>Polycystic kidneys<br>Arteriovenous malformation<br>Infarct<br>Hydronephrosis<br>Fistula | Anticoagulants<br>Coagulation defects<br>Sickle cell disease<br>Thromboembolism |

**Common Urologic Causes of Hematuria can be Classified as:**

**TICS**
**T**rauma/**T**umour/**T**oxins
**I**nfection/**I**nflammatory
**C**alculi/**C**ysts
**S**urgery/**S**ickle cell and other hematological causes

### History
- timing of hematuria in urinary stream
  - initial: anterior urethra
  - terminal: bladder neck, prostatic urethra
  - total: bladder and above
- presence of blood clots
- LUTS and associated symptoms
  - pyuria, dysuria: UTI
  - flank pain, radiation: ureteral obstruction
- last menstrual period, history of kidney stones, UTI, or previous urologic surgery
  - recent URTI, post-infectious glomerulonephritis, IgA nephropathy
- medications (anticoagulants, rifampin, phenazopyridine, phenytoin)
- risk factors for malignancy (smoking, chemical exposures, Hx of cyclophosphamide therapy, pelvic radiation)

### Investigations
- U/A, urine C&S, urine cytology
- imaging
  - lower tract: cystoscopy
  - upper tract: CT (gold standard), U/S
- CBC (rule out anemia, leukocytosis), electrolytes, Cr, BUN, INR, PTT, PSA (in men)

**Upper Tract Imaging Options**
**CT Urography (CTU):** test of choice for renal parenchyma, calculi, and infections. Involves exposure to radiation and IV contrast (assess renal function and allergies)
**U/S:** Superior to IVP for evaluation of renal parenchyma and renal cysts; limited sensitivity for UCC and small renal masses; U/S alone is insufficient for upper tract imaging
**Intravenous Pyelogram (IVP):** Traditional option but rarely used (replaced by CTU); reasonable sensitivity for UCC, but poor sensitivity for RCC

### Acute Management of Severe Bladder Hemorrhage
- manual irrigation via catheter with normal saline to remove clots
- Continuous Bladder Irrigation (CBI) using large (22-26 Fr) 3-way Foley to help prevent clot formation
  - should be done after manual irrigation of all clots
- cystoscopy
  - identify tumours or other source(s)
  - coagulate obvious sites of bleeding or transurethral resection of tumours (under general or regional anesthesia)

# Microscopic Hematuria

### Definition
- blood in the urine that is not visible to the naked eye
- >2 RBCs/HPF on urinalysis of at least two separate samples

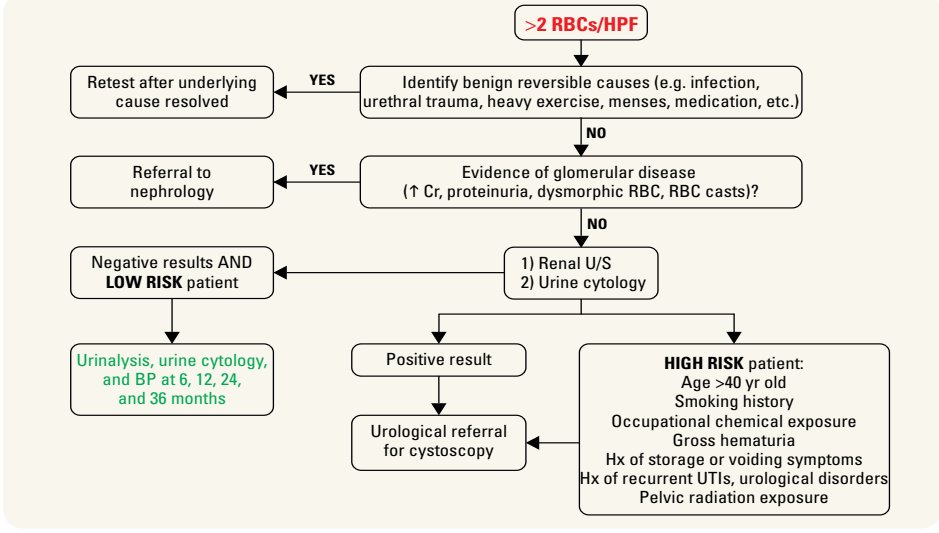



**Figure 8. Workup of asymptomatic microscopic hematuria**
Based on CUA Guidelines. Alternatively, the AUA recommends cystoscopy and CT urogram for all patients with confirmed microscopic hematuria; follow-up for negative workup is urinalysis yearly for two years, with repeat anatomic evaluation if microscopic hematuria persists

# Lower Urinary Tract Dysfunction

- two phases of lower urinary tract function
  1. storage phase (bladder filling and urine storage)
     - accommodation and compliance
     - no involuntary contraction(s)
  2. voiding phase (bladder emptying)
     - coordinated detrusor contraction
     - synchronous relaxation of outlet sphincters
     - no anatomic obstruction
- lower urinary tract dysfunction can therefore be classified as:
  - failure to store: due to bladder or outlet
  - failure to void: due to bladder or outlet
- three types of symptoms
  - storage (formerly known as irritative)
  - voiding (formerly known as obstructive)
  - post-voiding

**Transient Causes of Reversible Urinary Incontinence in the Elderly**

**DIAPERS**
**D**elirium
**I**nflammation/Infection
**A**trophic vaginitis/urethritis
**P**harmaceuticals/**P**sychological
**E**xcess U/O
**R**estricted mobility/**R**etention
**S**tool impaction

# Urinary Incontinence

## Definition
- involuntary leakage of urine

Urgency is the complaint of a sudden compelling desire to void that is difficult to defer; it is not necessarily associated with incontinence

## Epidemiology
- variable prevalence in women: 25-45%
- F:M = 2:1
- more frequent in the elderly, affecting 5-15% of those living in the community and 50% of nursing home residents

**Table 3. Urinary Incontinence: Types and Treatments**

| Type | Stress | Urgency | Mixed | Overflow |
|---|---|---|---|---|
| **Definition** | Leakage with sudden increases in intra-abdominal pressure (cough, sneeze, exertion) | Leakage preceded by strong, sudden urge to void | Leakage with urgency and increased intra-abdominal pressure | Leakage associated with urinary retention |
| **Etiology** | Sphincter incompetence<br>Urethral hypermobility<br>Common in middle aged and older women, and men following prostate cancer treatment or rarely surgical treatment of BPH | Detrusor overactivity<br>Bladder hypersensitivity | Same as stress and urgency incontinence | BPH with overflow incontinence<br>From weak bladder that does not empty (e.g. diabetic cystopathy) |
| **Investigations** | Hx: when leakage occurs, number of pads, LUTS, history of neurologic disease, pelvic surgery/radiotherapy, obstetrical history, bowel and sexual function, medications, impact on quality of life<br>P/E: general (edema, neurologic abnormalities, mobility, cognition, dexterity), abdomen (distended bladder), GU (prolapse in women, DRE in men), cough test<br>U/A, urine C&S, voiding diary (type of incontinence, how often, volume of leakage)<br>Urodynamics | | | See *Urinary Retention*, U7 |
| **Management** | Risk reduction: weight loss, smoking cessation<br>Kegel exercises<br>Urethral bulking agents<br>Surgery: urethral slings, or artificial sphincter in men | Conservative: fluid management, bladder training, Kegel exercises<br>Medication: anticholinergics, β-3 agonist<br>Botulinum toxin A bladder injection<br>Neuromodulation | Combination of management of stress and urgency incontinence | Catheterization<br>Treat underlying cause |

# Lower Urinary Tract Symptoms

## Urinary Retention

- storage symptoms (FUN): frequency, urgency (strong need to void), nocturia
- voiding symptoms (SHED): stream changes/straining, hesitancy, incomplete emptying, post-void dribbling

**Table 4. Etiology of Urinary Retention**

| Outflow Obstruction | Bladder Innervation | Pharmacologic | Infection |
|---|---|---|---|
| Bladder neck or urethra: calculus, clot, foreign body, neoplasm, neurological (DSD)<br>Prostate: BPH, prostate cancer<br>Urethra: stricture, phimosis, traumatic disruption<br>Miscellaneous: constipation, pelvic mass | Intracranial: CVA, tumour, Parkinson's, cerebral palsy<br>Spinal cord: injury, disc herniation, MS<br>DM<br>Post-abdominal or pelvic surgery | Anticholinergics<br>Narcotics<br>Antihypertensives (ganglionic blockers, methyldopa)<br>OTC cold medications containing ephedrine or pseudoephedrine<br>Antihistamines<br>Psychosomatic substances (e.g. ecstasy) | GU: UTI, prostatitis, abscess, genital herpes<br>Infected foreign body<br>Varicella zoster |

If a trauma patient is unable to void, has blood at urethral meatus, a scrotal hematoma, or a high riding prostate, there is urethral injury until proven otherwise so catheterization is CONTRAINDICATED unless performed by urology staff or resident

### Clinical Features

- suprapubic pain (with acute retention), incomplete emptying, weak stream
- palpable and/or percussible bladder (suprapubic)
- possible purulent/bloody meatal discharge (with UTI)
- increased size of prostate or reduced anal sphincter tone on DRE
- neurological: presence of abnormal or absent deep tendon reflexes, reduced "anal wink", saddle anesthesia

**Acute vs. Chronic Retention**
**Acute** retention is a medical emergency characterized by suprapubic pain and inability to void
**Chronic** retention can be painless with greatly increased bladder volume and detrusor hypertrophy followed by atony (late)

### Investigations

- CBC, electrolytes, Cr, BUN, U/A and urine C&S, U/S, cystoscopy, urodynamic studies, PVR

Patients with ascites may have a falsely elevated PVR measured by bladder scan

### Treatment

- treat underlying cause
- catheterization
  - acute retention
    - immediate catheterization to relieve retention; leave Foley in to drain bladder; follow-up to determine cause; closely monitor fluid status and electrolytes (risk of POD)
  - chronic retention
    - intermittent catheterization by patient may be used; definitive treatment depends on etiology
- suprapubic catheter if obstruction precludes urethral catheter
- for post-operative patients with retention:
  - encourage ambulation
  - α-blockers to relax bladder neck/outlet (men only)
  - may need catheterization
  - definitive treatment will depend on etiology

## Benign Prostatic Hyperplasia

### Definition

- periurethral hyperplasia of stroma and epithelium in prostatic transition zone
- prostatic smooth muscle cells play a role in addition to hyperplasia

### Etiology

- unknown
  - DHT required (converted from testosterone by 5-α reductase)
  - possible role of impaired apoptosis, estrogens, other growth factors

### Epidemiology

- age-related, extremely common (50% of 50 yr olds, 80% of 80 yr olds)
- 25% of men will require treatment

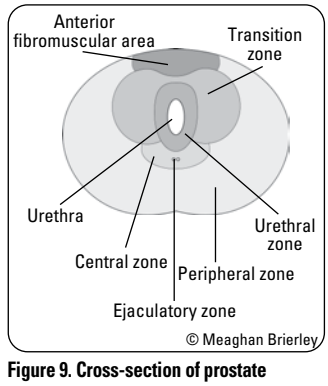



**Figure 9. Cross-section of prostate**

### Clinical Features

- result from outlet obstruction and compensatory changes in detrusor function
- voiding and storage symptoms
- DRE
  - prostate is smooth, rubbery, and may be symmetrically enlarged

Prostate size does not correlate well with symptoms in BPH

- complications
  - retention
  - overflow incontinence
  - hydronephrosis
  - renal insufficiency
  - infection
  - gross hematuria
  - bladder stones

### Investigations
- mandatory: Hx including LUTS, surgery, trauma, medications (OTC and phytotherapeutic agents), impact of QOL, P/E including DRE, U/A to exclude UTI
- recommended: symptom inventory (IPSS or AUA-SI), PSA if >10 yr life expectancy or if it changes management of voiding symptoms
- optional: Cr, urine cytology, uroflowmetry, PVR, voiding diary, sexual function questionnaire
- renal U/S to assess for hydronephrosis
- consider cystoscopy or bladder ultrasound prior to potential surgical management to evaluate outlet and prostate volume
- biopsy if suspicious for malignancy, i.e. elevated PSA or abnormal DRE

### Treatment

**Table 5. Treatment of BPH (see Table 28 and Figure 6 and 7)**

| | Conservative | Medical | Surgical | Minimally Invasive Surgical Therapies |
|---|---|---|---|---|
| **When to use** | Asymptomatic or mildly symptomatic, minimal bother | Moderately to severely symptomatic, bothersome | Absolute or relative indications, significant bother | Patients who wish to avoid or may not tolerate surgery |
| **Options** | Watchful waiting: 50% of patients improve spontaneously<br>Lifestyle modifications (e.g. evening fluid restriction, planned voiding) | α-adrenergic antagonists: reduce stromal smooth muscle tone<br>5-α reductase inhibitor: block conversion of testosterone to DHT; act to reduce prostate size<br>Combination is synergistic<br>Antimuscarinics or β-3 agonist (for storage LUTS, without elevated PVR)<br>PDE5 inhibitors (ED and for storage and voiding LUTS)<br>Desmopressin (LUTS with nocturia); risk of hyponatremia in ≥65 year old | TURP (see U43)<br>BPKVP (<60 cc)<br>Laser prostatectomy<br>TUIP (<30 cc)<br>Aquablation (new, <80 cc)<br>Open simple prostatectomy (>100 cc) | TUMT<br>UroLift (new, <80 cc)<br>Convective water vapour energy ablation (new)<br>Prostatic stent (for those unfit for surgery) |

**Approximate Prostate Sizes**
20 cc – chestnut
25 cc – plum
50 cc – lemon
75 cc – orange
300 cc – grapefruit

**AUA BPH Symptom Score**

**FUNWISE**
**F**requency
**U**rgency
**N**octuria
**W**eak stream
**I**ntermittency
**S**training
**E**mptying, incomplete feeling of

Each symptom graded out of 5
0-7: Mildly symptomatic
8-19: Moderately symptomatic
20-35: Severely symptomatic
Note: dysuria not included in score but is commonly associated with BPH

Initial alpha-adrenergic antagonist monotherapy for score <20, combination therapy for score >20

Men with planned cataract surgery should avoid starting α-adrenergic antagonists until after their surgery due to the risk of intraoperative floppy iris syndrome

**BPH Surgery**

**Absolute Indication**
Renal failure with obstructive uropathy
Refractory urinary retention

**Relative Indications**
Recurrent UTIs
Recurrent hematuria refractory to medical treatment
Renal insufficiency (rule out other causes)
Bladder stones
Severe symptoms unresponsive to medical therapies

# Urethral Stricture

### Definition
- decrease in urethral calibre due to scar formation in urethra (may also involve corpus spongiosum)
- M>F

### Etiology
- congenital
  - failure of normal canalization (i.e. posterior urethral valves)
- trauma
  - instrumentation/catheterization (most common)
  - external trauma (e.g. burns, straddle injury)
  - foreign body
- infection
  - long-term indwelling catheter
  - STI (gonococcal or chlamydial disease)
- inflammation
  - balanitis xerotica obliterans (BXO; lichen sclerosus or chronic progressive sclerosing dermatosis of the male genitalia) causing meatal and urethral stenosis
  - radiation
- malignancy (urothelial carcinoma)
  - most urethral cancers in men are squamous

### Clinical Features
- voiding and storage symptoms
- urinary retention
- hydronephrosis
- related infections: recurrent UTI, secondary prostatitis/epididymitis

### Investigations
- laboratory findings
  - flow rates <10 mL/s (normal >15 mL/s) on uroflowmetry
  - urine culture usually negative, but U/A may show pyuria
- radiologic findings
  - RUG and VCUG will demonstrate location
- cystoscopy

### Treatment
- urethral dilatation
  - temporarily increases lumen size by breaking up scar tissue
  - healing will often reform scar tissue, recurrence of stricture
- visual internal urethrotomy (VIU)
  - endoscopically incise stricture
  - equal success rates to dilation with mid bulbar strictures <2 cm
  - high rate of recurrence (30-80%), avoid in younger patients
- open surgical reconstruction (urethroplasty)
  - complete stricture excision with anastomosis depending on location and size of stricture
  - may require graft to reconstruct (e.g. buccal mucosa)

## Neurogenic Bladder

### Definition
- dysfunction of the urinary bladder due to deficiency in some aspect of its innervation

### Neurophysiology
- see Figure 6 and 7
- stretch receptors in the bladder wall relay information to PMC and activate micturition reflex (normally inhibited by cortical input)
  - micturition (voiding)
    - stimulation of parasympathetic neurons (bladder contraction)
    - inhibition of sympathetic and somatic neurons (internal and external sphincter relaxation, respectively)
    - voluntary relaxation of the pelvic floor and striated urethral sphincter
  - urine storage
    - opposite of micturition
- voluntary action of external sphincter (pudendal nerve roots S2-S4) can inhibit urge to urinate
- cerebellum, basal ganglia, thalamus, and hypothalamus all have input at PMC in the brainstem to inhibit the detrusor reflex

### Examples of Neurogenic Lower Urinary Tract Dysfunction
- neurogenic detrusor overactivity (NDO)(formerly termed detrusor hyperreflexia)
  - lesion above PMC (e.g. stroke, tumour, MS, Parkinson's disease)
  - loss of voluntary inhibition of voiding
  - intact pathway inferior to PMC maintains coordination of bladder and sphincter
- detrusor sphincter dyssynergia (DSD)
  - suprasacral lesion of spinal cord (e.g. trauma, MS, arteriovenous malformation, transverse myelitis)
  - loss of coordination between detrusor and sphincter (detrusor contracts on closed sphincter and vice versa)
  - component of detrusor overactivity as well
- detrusor atony/areflexia
  - lesion of sacral cord or peripheral efferents (e.g. trauma, DM, disc herniation, MS, congenital spinal cord abnormality, post abdominoperineal resection)
  - flaccid bladder which fails to contract
  - may progress to poorly compliant bladder with high pressures
- peripheral autonomic neuropathy
  - deficient bladder sensation → increasing residual urine → decompensation (e.g. DM, neurosyphilis, herpes zoster)
- muscular lesion
  - can involve detrusor, smooth/striated sphincter

**Combination Therapy vs. α-Blocker or 5ARI**
BJU Int 2011;107(6):946-54
**Summary**: Men with baseline prostate volume ≥40 mL and baseline PSA ≥1.5 ng/mL had greater reductions in RR of BPH-related surgery and RR of clinical progression on combined therapy or dutasteride monotherapy than on tamulosin monotherapy.
**Methods**: 4 year combination of dutasteride and tamulosin study was a multicentre double-blind RCT of outcomes in men ≥50 years old with symptomatic BPH, with PSA ≥1.5 ng/mL and ≤10ng/mL, and prostate volume ≤30 mL. Patients received tamulosin, dutasteride or combination therapy. Primary endpoint was time to first acute urinary retention or BPH-related surgery; secondary endpoint was clinical progression of BPH/symptoms.
**Results**: Combination therapy resulted in significantly greater improvements in symptoms compared to dutasteride from 3 mo, and tamsulosin from 9 mo, and in BPH-related health status from 3 and 12 mo, respectively. There was a significant increase in ADE with combination therapy vs. monotherapies. However, withdrawal rates due to drug-related adverse events were similar across the treatment groups.

**Finasteride for Benign Prostatic Hyperplasia**
Cochrane DB Syst Rev 2010;10:CD006015
**Purpose**: To examine the effectiveness and safety of finasteride versus placebo or other active controls for the treatment of urinary tract symptoms.
**Summary of Findings**:
1. Finasteride improved urinary symptoms more than placebo in trails >1 yr duration and significantly lowered the risk of BPH progression.
2. Compared with α-blockers, finasteride was less effective than either doxazosin or terazosin, but equally as effective as tamsulosin.
3. Symptom improvement with finasteride + doxazosin is equal to doxazosin alone.
4. Finasteride treatment resulted in an increased risk of ejaculation disorder, impotence and lowered libido compared with placebo.
5. Compared with doxazosin and terazosin, finasteride had a lower risk of asthenia, dizziness, and postural hypotension.

Nerve roots in micturition:
**"S2-3-4 keeps the urine off the floor"**

### Neuro-Urologic Evaluation

- Hx and P/E (urologic and general neurologic)
- voiding diary
- catheterization volumes in patients with CIC
- U/A, renal profile
- imaging
  - U/S to rule out hydronephrosis and stones; occasionally CT scanning with or without contrast
- cystoscopy
- urodynamic studies
  - uroflowmetry to assess flow rate, pattern
  - filling CMG to assess capacity, compliance, detrusor overactivity
  - voiding CMG (pressure-flow study) to assess bladder contractility and extent of bladder outflow obstruction
  - video study to visualize bladder/bladder neck/urethra during CMG using x-ray contrast
  - EMG and video ascertains presence of coordinated or uncoordinated voiding, allows accurate diagnosis of DSD

"Spinal shock" initially manifests as atonic bladder

### Treatment

- goals of treatment
  - prevent renal deterioration
  - prevent infections
  - achieve social continence
- clean intermittent catheterization (CIC) (if there is associated inability to void)
- treatment options depend on status of bladder and urethra
  - bladder hyperactivity → antimuscarinic medications to relax bladder (see *Urinary Incontinence*, U6)
    - if refractory
      - botulinum toxin injections into bladder wall (detrusor muscle)
      - occasionally augmentation cystoplasty (enlarging bladder volume and improving compliance by grafting section of detubularized bowel onto the bladder)
      - occasionally urinary diversion (ileal conduit or continent diversion) in severe cases if bladder management unsuccessful
  - flaccid bladder → CIC

## Dysuria

### Definition

- painful urination

### Etiology

**Table 6. Differential Diagnosis of Dysuria**

| | |
|---|---|
| **Infectious** | Cystitis, urethritis, prostatitis, epididymitis/orchitis (if associated with lower tract inflammation), cervicitis, vulvovaginitis, perineal inflammation/infection, TB, vestibulitis |
| **Neoplasm** | Kidney, bladder, prostate, penis, vagina/vulva, BPH |
| **Calculi** | Bladder stone, urethral stone, ureteral stone |
| **Inflammatory** | Seronegative arthropathies (reactive arthritis: arthritis, uveitis, urethritis), drug side effects, autoimmune disorders, chronic pelvic pain syndrome (CPPS), interstitial cystitis |
| **Hormonal** | Endometriosis, hypoestrogenism |
| **Trauma** | Catheter insertion, post-coital cystitis (honeymoon cystitis) |
| **Psychogenic** | Somatization disorder, depression, stress/anxiety disorder |
| **Other** | Contact sensitivity, foreign body, radiation/chemical cystitis, diverticulum |

### Investigations

- focused Hx and P/E to determine cause (fever, d/c, conjunctivitis, CVA tenderness, back/joint pain)
  - any d/c (urethral, vaginal, cervical) should be sent for gonococcus/chlamydia testing; wet mount if vaginal d/c
  - U/A and urine C&S
  - if suspect infection, may start empiric ABx treatment (see Table 9)
  - ± imaging of urinary tract (tumour, stones)

# Hydronephrosis

### Definition
- the upper urinary tract consists of the kidneys and ureters
- dilation of the renal pelvis and calyces caused by the impairment in antegrade urine flow (aka pelvicaliectasis)

### Etiology
- mechanical
  - congenital: see *Congenital Abnormalities*, U37
  - acquired
    - intrinsic: trauma, inflammation and bleeding, calculi, urologic neoplasms, BPH, urethral stricture, phimosis, previous urological surgery
    - extrinsic: trauma, neoplasms (uterine fibroid; colorectal, uterine, and cervical malignancies; lymphoma), aortic aneurysm, pregnancy (gravid uterus)
- functional
  - neuropathic: neurogenic bladder, diabetic neuropathy, spinal cord disease
  - hormonal: pregnancy (progesterone decreases ureteral tone)

### Investigations
- focused Hx, inquiring about pain (flank, lower abdomen, testes, labia), U/O, medication use, pregnancy, trauma, fever, Hx of UTIs, calculi, PID, and urological surgery
- CBC, electrolytes, Cr, BUN, U/A, urine C&S
- imaging studies (U/S is >90% sensitive and specific)
  - CT: helps delineate anatomy and potential causes (e.g. obstructing stone), but does not provide much functional information
  - MAG3 diuretic renogram: provides little anatomic structural information but evaluates differential renal function and demonstrates if functional obstruction exists

### Treatment
- hydronephrosis can be physiologic (e.g. pregnancy)
- treatment should be guided at improving symptoms, treating infections, or improving renal function
- urgent treatment may require percutaneous nephrostomy tube or ureteral stenting to relieve pressure

# Post-Obstructive Diuresis

### Definition
- polyuria resulting from relief of obstructive uropathy (i.e. elevated creatinine)
- >3 L/24 h or >200 cc/h over each of two consecutive hours

### Pathophysiology
- physiologic POD secondary to excretion of retained urea, $Na^+$, and $H_2O$ (high osmotic load) after relief of obstruction
  - self-limiting; usually resolves in 48 h with PO fluids but may persist to pathologic POD
- pathologic POD is a $Na^+$-wasting nephropathy secondary to impaired concentrating ability of the renal tubules due to:
  - decreased reabsorption of NaCl in the thick ascending limb and urea in the collecting tubule
  - increased medullary blood flow (solute washout)
  - increased flow and solute concentration in the distal nephrons

### Management
- admit patient and closely monitor hemodynamic status and electrolytes ($Na^+$ and $K^+$ q6-12h and replace prn; follow Cr and BUN to baseline)
- monitor U/O q2h and ensure total fluid intake <U/O by replacing every 1 mL U/O with 0.5 mL 1/2 NS IV (PO fluids if physiologic POD)
- avoid glucose-containing fluid replacement (iatrogenic diuresis)

# Overactive Bladder

## Definition
- a symptom complex that includes urinary urgency with or without urgency incontinence, urinary frequency (voiding ≥8 times in a 24 h period), and nocturia (awakening ONE or more times at night to void)

## Etiology
- multiple etiologies proposed (neurogenic, myogenic, idiopathic)
- symptoms usually associated with involuntary contractions of the detrusor muscle
- may be associated with other conditions such as SUI in women and BPH in men (see Table 5)

## Epidemiology
- F:M= 1:1
- prevalence increases with age. 42% in males ≥75 years; 31% in females ≥75 years
- women experience incontinence more commonly than men

## Diagnosis
- the diagnostic process should document symptoms that define overactive bladder and exclude other disorders that could cause of the patient's symptoms
- minimal requirements for the process consist of:
  - focused history including past genitourinary disorders and conditions outlined in Table 7, questionnaires of LUTS and diaries of urination frequency, volume and pattern
  - P/E including genitourinary, pelvic and rectal examination
  - U/A to rule out hematuria and infection
- in some patients, the following investigations could be considered
  - post-void residual
  - cystoscopy to rule out recurrent infections, carcinoma in situ and other intravesical abnormalities
- urodynamics to rule out obstruction in older men

## Treatment
- non-pharmacological: behaviour therapies such as bladder training, bladder control strategies, pelvic floor muscle training, fluid management, and avoidance of caffeine and alcohol
- pharmacological (see Table 29)
  - anti-muscarinics: oxybutynin hydrochloride, tolterodine, solifenacin, fesoterodine, darifenacin, propiverine or trospium
  - β3-adrenoceptor agonist: mirabegron
- refractory patients may be treated with:
  - neuromuscular-junction inhibition: botulinum toxin bladder injection
- others
  - percutaneous tibial nerve stimulation (not used commonly in Canada)
  - sacral neuromodulation

**Table 7. Conditions that Could Contribute to Symptoms of Overactive Bladder**

| | |
|---|---|
| **Lower Urinary Tract Conditions** | UTI, obstruction, impaired bladder contractility |
| **Neurological Conditions** | Stroke, MS, dementia, diabetic neuropathy |
| **Systemic Diseases** | CHF, sleep disorders (primarily nocturia) |
| **Functional and Behavioural** | Excessive caffeine and alcohol, constipation, impaired mobility |
| **Medication** | Diuretics, anticholinergic agents, narcotics, calcium-channel blocker, cholinesterase inhibitors |

# Infectious and Inflammatory Diseases

**Table 8. Antibiotic Treatment of Urological Infections**

| Condition | Drug | Duration |
|---|---|---|
| **Urethritis** | **Non-Gonococcal** | |
| | azithromycin (1 g PO) | x 1 d |
| | OR | |
| | doxycycline (100 mg PO bid) | 7 d |
| | **Gonococcal** | |
| | ceftriaxone (250 mg IM) AND treat for *Chlamydia trachomatis* | x 1 |
| **Simple, Uncomplicated UTI** | TMP-SMX (160 mg/800 mg PO bid) | 3 d |
| | OR | |
| | nitrofurantoin (100 mg PO bid) | 5 d |
| **Complicated UTI** | ciprofloxacin (1 g PO daily OR 400 mg IV q12h) | up to 2-3 wk |
| | OR | |
| | ampicillin (1 g IV q6h) + gentamicin (1 mg/kg IV q8h) (used for relatively short courses because of toxicity) | up to 2-3 wk |
| | OR | |
| | ceftriaxone (1-2 g IV q24h) | up to 2-3 wk |
| **Recurrent/Chronic Cystitis** | Prophylactic Treatment | |
| | Continuous: TMP-SMX (40 mg/200 mg PO qHS OR 3x/wk) | 6-12 mo |
| | OR | |
| | nitrofurantoin (50-100 mg PO qHS) | 6-12 mo |
| | Post-Coital: TMP-SMX (40 mg/200 mg-80 mg/400 mg) | within 2 h of coitus |
| | OR | |
| | nitrofurantoin (50-100 mg PO qd) | within 2 h of coitus |
| **Acute Prostatitis** | ciprofloxacin (500-750 mg PO bid) | 2-4 wk |
| | OR | |
| | TMP-SMX (160 mg/800 mg PO bid) | 4 wk |
| | OR | |
| | IV therapy with gentamicin and ampicillin, penicillin with β-lactamase inhibitor, 3rd gen cephalosporin, OR a fluoroquinolone | 4 wk (IV and oral step-down) |
| **Chronic Prostatitis** | ciprofloxacin (500 mg PO bid) | 4-6 wk |
| **Epididymitis/Orchitis** | <35 yr | |
| | ceftriaxone (200 mg IM) | x 1 |
| | AND | |
| | doxycycline (100 mg PO bid) | 10 d |
| | ≥35 yr | |
| | ofloxacin (300 mg PO bid) | 10 d |
| **Acute Uncomplicated Pyelonephritis** | ciprofloxacin (500 mg PO bid) | 7 d |
| | ± ceftriaxone (1 g IV) OR ciprofloxacin (400 mg IV) | x 1 |
| | OR | |
| | IV therapy with a fluoroquinolone, gentamicin and ampicillin, extended spectrum cephalosporin, extended spectrum penicillin, OR a carbapenem | 14 d total IV and oral step-down |

Antibiotic therapy should always be based on local resistance patterns and adjusted according to culture and sensitivity results

Acute uncomplicated pyelonephritis: suspected or confirmed *Enterococcus* infection requires treatment with ampicillin

## Urinary Tract Infection

- for UTIs during pregnancy, see Obstetrics, OB29

### Definition

- symptoms suggestive of UTI + evidence of pyuria and bacteriuria on U/A or urine C&S
  - if asymptomatic + 100,000 CFU/mL = asymptomatic bacteriuria; only requires treatment in certain patients (e.g. pregnancy, immunosuppressed, prior to urologic surgery)

### Classification

- uncomplicated: lower UTI in a setting of functionally and structurally normal urinary tract
- complicated: structural and/or functional abnormality, male patients, immunocompromised, diabetic, iatrogenic complication, pregnancy, pyelonephritis, catheter-associated
- recurrent: see *Recurrent/Chronic Cystitis*, U14

### Risk Factors

- stasis and obstruction
  - residual urine due to impaired urine flow e.g. PUVs, reflux, medication, BPH, urethral stricture, cystocele, neurogenic bladder
- foreign body
  - introduce pathogen or act as nidus of infection e.g. catheter, instrumentation

- decreased resistance to organisms
  - DM, malignancy, immunosuppression, spermicide use, estrogen depletion, antimicrobial use
- other factors
  - trauma, anatomic abnormalities, female, sexual activity, menopause, fecal incontinence

### Clinical Features
- storage symptoms: frequency, urgency
- voiding symptoms: hesitancy, post-void dribbling, dysuria
- other: suprapubic pain, hematuria, foul-smelling urine
- pyelonephritis – if present: typically presents with more severe symptoms (e.g. fever/chills, CVA tenderness, flank pain)

### Indications for Investigations
- pyelonephritis
- persistence of pyuria/symptoms following adequate antibiotic therapy
- severe infection with an increase in Cr
- recurrent/persistent infections
- atypical pathogens (urea splitting organisms)
- Hx of structural abnormalities/decreased flow

### Investigations
- U/A, urine C&S
  - U/A: leukocytes ± nitrites ± hematuria
  - C&S: midstream, catheterized, or suprapubic aspirate
- if hematuria present, retest post-treatment, if persistent need hematuria workup (see *Microscopic Hematuria*, U5)
- U/S, CT scan if recurrent or treatment-resistant UTIs, suspected anatomic abnormalities, history indicates complicated cystitis

### Treatment
- see Table 8, U13, *Antibiotic Treatment of Urological Infections*
- if febrile, consider admission with IV therapy and rule out obstruction

### Prevention of UTIs
- maintain good hydration (emerging evidence re: cranberry preparations)
- void regularly (do not hold urine for prolonged periods of time)
- wipe from front to back to avoid contamination of the urethra with feces from the rectum
- avoid feminine hygiene sprays and scented douches
- empty bladder immediately before and after intercourse

**Prevention of UTIs**
- Maintain good hydration (try cranberry preparations)
- Wipe from front to back to avoid contamination of the urethra with feces from the rectum
- Avoid feminine hygiene sprays and scented douches
- Empty bladder immediately before and after intercourse

### Organisms
- typical organisms: SEEK PP (*E. coli* 75-95%)
- atypical organisms
  - tuberculosis (TB)
  - *Chlamydia trachomatis*
  - *Mycoplasma (Ureaplasma urealyticum)*
  - fungi (*Candida*)

## Recurrent/Chronic Cystitis

### Definition
- ≥3 UTIs/yr

### Etiology
- bacterial reinfection (80%) vs. bacterial persistence (relapse)
  - bacterial reinfection
    - recurrence of infection with either 1) a different organism, 2) the same organism if cultured >2 wk following therapy, or 3) with any organism with an intermittent sterile culture
  - bacterial persistence
    - same organism cultured within 2 wk of sensitivity-based therapy

### Investigations
- assess predisposing factors
- investigations may include cystoscopy, U/S, CT

### Treatment
- lifestyle changes (limit caffeine intake, increase fluid/$H_2O$ intake)
- ABx (various strategies): continuous low-dose daily suppression vs. post-coital only vs. self-start therapy
- post-menopausal women: consider topical or systemic estrogen therapy
- no treatment for asymptomatic bacteriuria except in pregnant women or patients undergoing urinary tract instrumentation

# Interstitial Cystitis (Painful Bladder or Bladder Pain Syndrome)

### Definition
- bladder pain, chronic urgency, and frequency without other identifiable causation

### Classification
- non-ulcerative (more common) and ulcerative

### Etiology
- unknown

### Epidemiology
- prevalence: 20/100,000
- 90% of cases are in females, 94% are Caucasian
- median age is 40 yr (non-ulcerative seen in younger to middle-aged, while ulcerative seen in middle-aged to older)

### Clinical Features
- pelvic pain (typically supra-pubic tenderness)
- storage symptoms (frequency > urgency > nocturia)
- negative U/A, urine C&S, urine cytology
- cystoscopy: glomerulations (submucosal petechiae), Hunner's lesions



Cystoscopic evaluation is not necessary to make a diagnosis

### Differential Diagnosis
- Uro: non-infectious cystitis (radiation, chemical, eosinophilic, TB), OAB, bladder calculi, prostate-related pain
- Gyne: endometriosis, vulvar disorders
- Neuro: pudendal nerve entrapment
- MSK: pelvic floor disorders
- Drugs: ketamine, tiaprofenic acid

### Investigations
- Hx, P/E, frequency volume chart
- symptom scores to establish baseline and response to treatment
- U/A, urine C&S, urine cytology
- cystoscopy

### Treatment
- first line: patient education, dietary modifications, bladder retraining, stress management
  - pelvic floor physiotherapy can be added for patients with pelvic floor dysfunction or pelvic pain
- second line: guided by symptom phenotype
  - oral: amitriptyline, cimetidine, hydroxyzine, pentosan polysulfate (PPS), gabapentin, quercetin
  - intravesical: dimethylsulfoxide (DMSO), heparin, lidocaine, PPS, oxybutynin
- third line: hydrodistension, botulinum toxin A, sacral neuromodulation
  - endoscopic treatment if Hunner's lesions (cauterization, resection, triamcinolone injection)
- fourth line: radical surgery (substitution cystoplasty or urinary diversion ± cystectomy)

# Acute Pyelonephritis

### Definition
- infection of the renal parenchyma with local and systemic manifestations
- clinical diagnosis of flank pain, fever and elevated WBC

### Etiology
- ascending (usually GN bacilli) or hematogenous route (usually GP cocci)
- causative microorganisms
  - Gram positives: *Enterococcus faecalis, S. aureus, S. saphrophyticus*
  - Gram negatives: *E. coli, Klebsiella, Proteus, Pseudomonas, Enterobacter*
- common underlying causes of pyelonephritis
  - stones, strictures, prostatic obstruction, vesicoureteric reflux, neurogenic bladder, catheters, DM, sickle-cell disease, PCKD, immunosuppression, post-renal transplant, instrumentation, pregnancy

### Clinical Features
- rapid onset (<24 h)
- LUTS including frequency, urgency, hematuria; NOT dysuria unless concurrent cystitis
- fever, chills, nausea, vomiting, myalgia, malaise
- CVA tenderness and/or exquisite flank pain

### Investigations
- U/A, urine C&S
- CBC and differential: leukocytosis, left shift
- imaging if complicated pyelonephritis or symptoms do not improve with 48-72 h of treatment
  - abdominal/pelvic U/S
  - CT
- nuclear medicine: DMSA scan can be used to help secure the diagnosis
  - a photopenic defect indicates active infection or scar; if normal alternative diagnoses should be considered

### Treatment
- hemodynamically stable
  - outpatient oral ABx treatment ± single initial IV dose (see Table 8, U13)
- severe or non-resolving
  - admit, hydrate, and treat with IV ABx (see Table 8, U13)
- emphysematous pyelonephritis
  - most patients receive nephrectomy after IV ABx started and patient stabilized
  - consider temporization with nephrostomy tubes
- renal obstruction
  - admit for emergent stenting or percutaneous nephrostomy tube

## Prostatitis/Prostatodynia

### Epidemiology
- prevalence: 9% of men/year, 6% with bothersome symptoms
- most common urologic diagnosis in men <50, 3rd most common in men >50

### Classification

**Table 9. Comparison of the Four Types of Prostatitis**

| | Acute Bacterial Prostatitis (Category I) | Chronic Bacterial Prostatitis (Category II) | Chronic Pelvic Pain Syndrome (Category III) | Asymptomatic Prostatitis (Category IV) |
|---|---|---|---|---|
| **Etiology** | Acute infection<br>SEEK PP (80% *E. coli*) | Chronic infection ± prostatitis symptoms | Symptoms without evidence of infection<br>IIIA: inflammatory<br>IIIB: non-inflammatory | Incidental inflammation |
| **Clinical Features** | LUTS, pelvic pain<br>Systemic signs: fever, chills, malaise<br>Leukocytosis in prostatic fluid<br>Positive bacterial cultures | LUTS, pelvic pain<br>No systemic signs<br>Recurrent UTIs<br>Leukocytosis in prostatic fluid<br>Positive bacterial cultures | LUTS, pelvic pain<br>IIIA: leukocytosis in prostatic fluid<br>IIIB: no leukocytosis in prostatic fluid | No symptoms<br>Leukocytosis in prostatic fluid |
| **Investigations** | Hx, P/E (abdo, external genitalia, perineum, prostate)<br>U/A, urine C&S<br>TRUS if suspect abscess | Hx, P/E (same as Category I + pelvic floor)<br>4 glass test for culture:<br>VB1 (urethra)<br>VB2 (bladder)<br>EPS (post-massage)<br>VB3 (post-massage) | Hx, P/E (same as Category II)<br>Symptom score (NIH-CPSI*)<br>4-glass test<br>Consider psychological assessment | No investigations unless considering ABx for elevated PSA or infertility |
| **Treatment** | ABx (see Table 8, U13)<br>Catheterization if severe obstructive<br>Drainage if abcess is present | ABx (see Table 8, U13)<br>α-blocker if obstruction | Supportive measures<br>ABx if ABx naïve<br>Multimodal therapy (UPOINT), including:<br>α-blockers<br>Anti-inflammatories<br>Phytotherapy (quercetin, cernilton) | ABx if elevated PSA, infertility, or planned prostate biopsy |

*NIH-CPSI: National Institute of Health Chronic Prostatitis Symptom Index

# Epididymitis and Orchitis

## Etiology
- common infectious causes
  - <35 yr: *N. gonorrhoeae* or *Chlamydia trachomatis*
  - ≥35 yr or penetrative anal intercourse: GI organisms (especially *E. coli*)
- other causes
  - mumps infection may involve orchitis, post-parotitis
  - TB
  - syphilis
  - granulomatous (autoimmune) in elderly men
  - amiodarone (involves only head of epididymis)
  - chemical: reflux of urine into ejaculatory ducts

## Risk Factors
- UTI
- unprotected sexual contact
- instrumentation/catheterization
- increased pressure in prostatic urethra (straining, voiding, heavy lifting) may cause reflux of urine along vas deferens → sterile epididymitis
- immunocompromise



If unsure between diagnoses of epididymitis and torsion, always go to OR
**Remember**: torsion >6 h has poor prognosis

## Clinical Features
- sudden onset scrotal pain and swelling ± radiation along cord to flank
- scrotal erythema and tenderness
- Prehn's Sign (relief of pain with lifting of testicle)
- fever
- storage symptoms, purulent d/c
- reactive hydrocele

## Investigations
- U/A, urine C&S
- ± urethral d/c: Gram stain/culture
- if diagnosis uncertain, MUST rule out testicular torsion (U/S Doppler)

## Treatment
- rule out torsion (see *Investigations* Table 23, U31)
- see Table 8, U13 for ABx therapy
- scrotal support, bed rest, ice, analgesia

## Complications
- if severe → testicular atrophy
- 30% have persistent infertility problems
- inadequately treated acute epididymitis may lead to chronic epididymitis or epididymo-orchitis

# Urethritis

## Etiology
- infectious or inflammatory (e.g. reactive arthritis)

**Table 10. Infectious Urethritis: Gonococcal vs. Non-Gonococcal**

| | Gonococcal | Non-Gonococcal |
|---|---|---|
| **Causative Organism** | *Neisseria gonorrhoeae* | Usually *Chlamydia trachomatis* |
| **Diagnosis** | Hx of sexual contact, thick, profuse, yellow-grey purulent d/c, LUTS<br>Gram stain (GN diplococci), urine PCR and/or culture from urethral specimen | Hx of sexual contact, mucoid whitish purulent d/c, ± storage LUTS<br>Gram stain demonstrates >4 PMN/oil immersion field, no evidence of *N. gonorrhoeae*, urine PCR and/or culture from urethral specimen |
| **Treatment** | See Table 8, U13 | See Table 8, U13 |



**Reactive Arthritis (formerly known as Reiter's syndrome)**
Urethritis, uveitis (or conjunctivitis), and arthritis
**(can't pee, can't see, can't climb a tree)**



If culture negative or unresponsive to treatment consider: *Ureaplasma urealyticum, Mycoplasma genitalium, Trichimonas vaginalis*, HSV, or adenovirus

# Stone Disease

## Epidemiology
- prevalence: ~8% and increasing
- M:F = 2:1
- peak incidence 30-50 yr of age
- recurrence rate: 10% at 1 yr, 50% at 5 yr, 60-80% lifetime

## Risk Factors
- hereditary: RTA, Glucose-6-phosphate dehydrogenase deficiency, cystinuria, xanthinuria, oxaluria, etc.
- lifestyle: minimal fluid intake; excess vitamin C, oxalate, purines, calcium
- medications: loop diuretics (furosemide, bumetanide), acetazolamide, topiramate, zonisamide, indinavir, acyclovir, sulfadiazine, triamterene
- medical conditions: UTI (with urea-splitting organisms: *Proteus, Pseudomonas, Providencia, Klebsiella, Mycoplasma, Serratia, S. aureus*), myeloproliferative disorders, IBD, gout, DM, hypercalcemia disorders (hyperparathyroidism, tumour lysis syndrome, sarcoidosis, histoplasmosis), obesity (BMI >30)
- bladder stones: bladder outlet obstruction, catheters, neurologic disease, DM (requires different management)

**Key Points in Stone Hx**
- Diet (especially FLUID INTAKE)
- Predisposing medical conditions
- Predisposing medications
- Previous episodes/investigations/treatments
- Family Hx (1st degree relative)

## Clinical Features
- urinary obstruction → upstream distention → pain
  - flank pain from renal capsular distention (non-colicky)
  - severe waxing and waning pain radiating from flank to groin, testis, or tip of penis from distended collecting system or ureter (ureteral colic)
- writhing, persistent discomfort, nausea, vomiting, hematuria (90% microscopic), diaphoresis, tachycardia, tachypnea
- occasionally symptoms of trigonal irritation (frequency, urgency), if the stone is in the lower ureter
- bladder stones result in: storage and voiding LUTS, terminal hematuria, suprapubic pain
- if fever, rule out concurrent pyelonephritis and/or obstruction
- can also present incidentally, without any pain or symptoms

**The Four Narrowest Passage Points for Upper Tract Stones**
- UPJ
- Pelvic brim
- Under vas deferens/broad ligament
- UVJ

**Table 11. Differential Diagnosis of Renal Colic**

| GU | Abdominal | Neurological |
|---|---|---|
| Pyelonephritis<br>Ureteral obstruction from other cause: UPJ obstruction, clot colic secondary to gross hematuria, sloughed papillae<br>Gynecological: ectopic pregnancy, torsion/rupture of ovarian cyst, PID | AAA<br>Bowel ischemia<br>Pancreatitis<br>Other acute abdominal crisis (appendicitis, cholecystitis, diverticulitis) | Radiculitis (L1): herpes zoster, nerve root compression |

## Location of Stones
- calyx: may cause flank discomfort, persistent infection, persistent hematuria, or remain asymptomatic
- pelvis: tend to cause obstruction at UPJ, may cause persistent infection
- ureter: <5 mm diameter will pass spontaneously in 75% of patients

| | Radiopaque | Radiolucent |
|---|---|---|
| **KUB** | Calcium<br>Struvite<br>Cystine | Uric acid<br>Indinavir<br>Atazanavir |
| **CT** | Calcium<br>Struvite<br>Cystine<br>Uric acid | Indinavir<br>Atazanavir |

## Stone Pathogenesis
- supersaturation of stone constituents (at appropriate temperature and pH)
- stasis, low flow, and low volume of urine (dehydration)
- crystal formation and stone nidus
- loss of inhibitory factors
  - citrate (forms soluble complex with calcium)
  - magnesium (forms soluble complex with oxalate)
  - pyrophosphate
  - Tamm-Horsfall glycoprotein

# Approach to Renal Stones

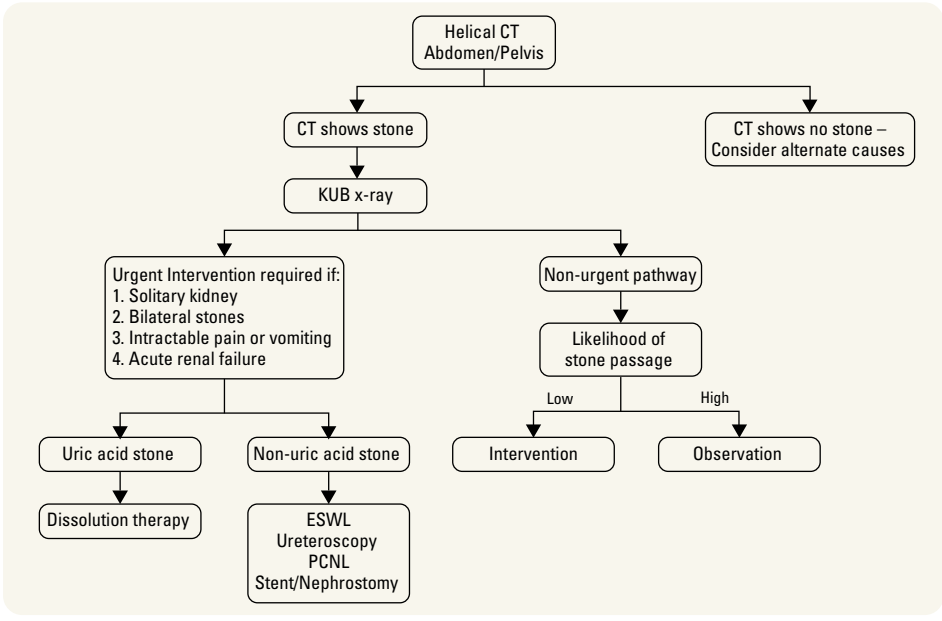



**Figure 10. Approach to renal stone**

Although hypercalciuria is a risk factor for stone formation, decreasing dietary calcium is NOT recommended to prevent stone formation. Low dietary calcium leads to increased GI oxalate absorption and higher urine levels of calcium oxalate

**Stones and Infection**
If septic, urgent decompression via ureteric stent or percutaneous nephrostomy is indicated. Definitive treatment of the stone should be delayed until the sepsis has cleared

**Indications for PCNL**
- Size >2 cm
- Staghorn
- UPJ obstruction with correction of obstruction
- Calyceal diverticulum
- Cystine stones (poorly fragmented with ESWL)
- Anatomical abnormalities
- Failure of less invasive modalities

## Investigations

**Table 12. Investigations for Renal Stones**

| | CBC, U/A, Urine C&S | KUB X-ray | CT Scan | Abdominal Ultrasound | Cystoscopy | Uric Acid | PTH, 24 h urine x 2 for volume, Cr, $Ca^{2+}$, $Na^{+}$, $PO_4^{3-}$, $Mg^{2+}$, oxalate, citrate, ± cystine |
|---|---|---|---|---|---|---|---|
| **Who gets it?** | Everyone | Most | First episode renal colic | Pediatric cases or those concerning for obstruction | ± Those concerning for bladder stone | Stone not seen on KUB | Recurrent $Ca^{2+}$ stone formers ± pediatric cases |
| **Why is it done?** | May show signs of infection, ± sensitivities | 90% of stones are radiopaque<br>Good for follow-up | Distinguish radiolucent stone from soft tissue filling defect<br>X-ray comparison | Identify and follow-up stone without radiation exposure<br>Visualize hydronephrosis | Visualize bladder | Suspected uric acid stone | Need to rule out metabolic cause for stones |
| **Cautions** | — | Do not mistake phleboliths for stones! | Radiation (especially if female of child bearing age)<br>Must be a non-contrast scan | — | — | | — |

## Treatment

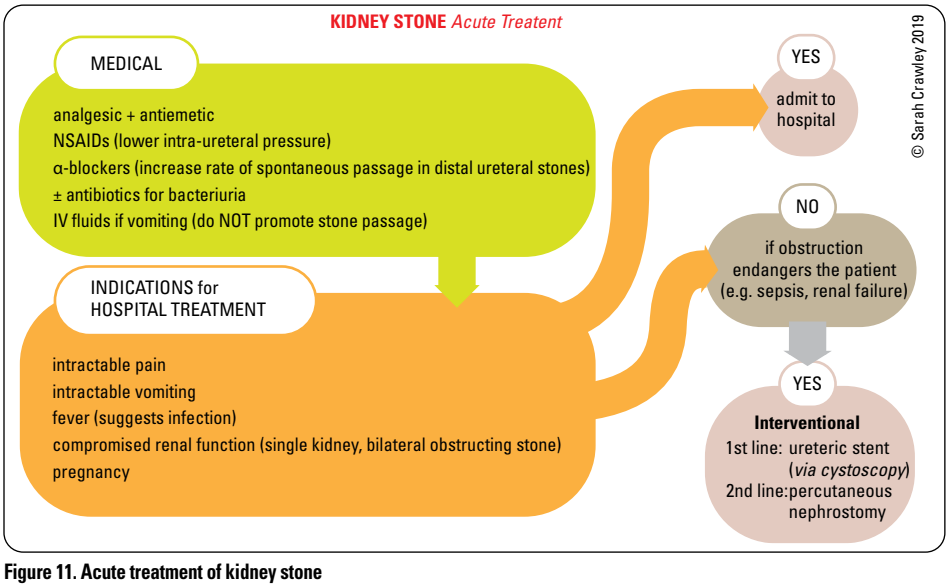



**Figure 11. Acute treatment of kidney stone**

24 h urine collections must be done AFTER discontinuing stone preventing/promoting medications

Detailed metabolic studies are NOT recommended unless complex patient (recurrent stone formers, pregnancy, pediatrics, strong family Hx, underlying kidney or systemic disease, etc.)

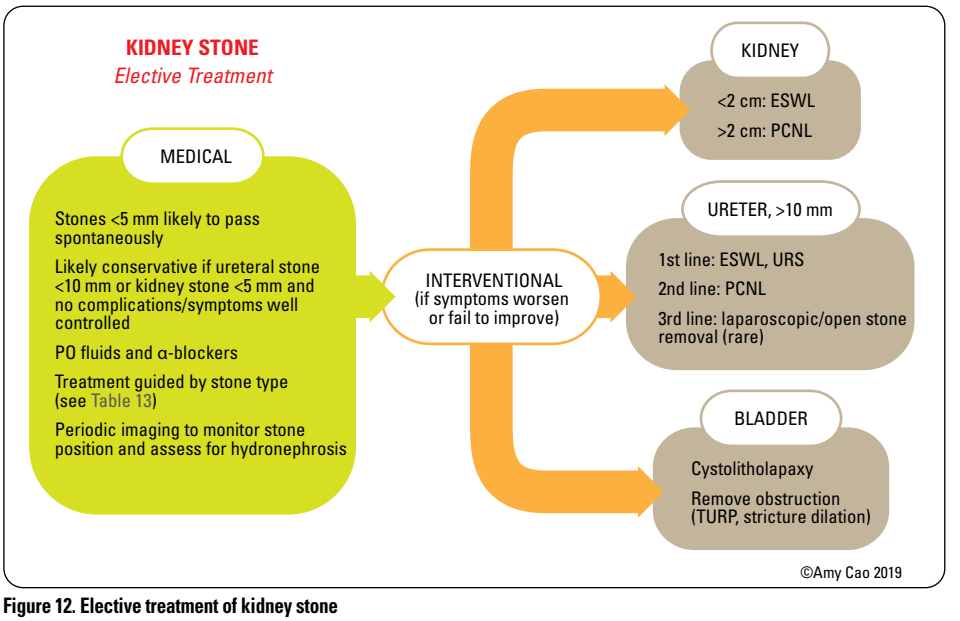



**Figure 12. Elective treatment of kidney stone**

**α-Blockers as Medical Expulsive Therapy for Ureteral Stones**
Cochrane DB Syst Rev 2018;4:CD008509
**Purpose**: To assess effects of α-blockers compared with standard therapy for ureteral stones 1 cm or smaller in adult patients presenting with symptoms of ureteral stone disease.
**Methods**: meta-analysis of 67 RCTs for ureteral stone passage in 10,509 adult patients.
**Results**: Treatment with an α-blocker resulted in increased stone clearance (risk ratio (RR) 1.45, 95% confidence interval (CI) 1.36 to 1.55; low-quality evidence). Subgroup analyses suggest that α-blockers may be less effective for smaller (5 mm or smaller) than for larger stones (greater than 5 mm).
**Conclusions**: α-blockers likely increase stone clearance, but also slightly increase the risk of major adverse events.

## Prevention

- dietary modification
  - increase fluid (>2 L/d), $K^+$ intake
  - reduce animal protein, oxalate, $Na^+$, sucrose, and fructose intake
  - avoid high-dose vitamin C supplements
- medications
  - thiazide diuretics for hypercalciuria
  - allopurinol for hyperuricosuria
  - potassium citrate for hypocitraturia, hyperuricosuria

### Table 13. Stone Classification

| Type of Stone | Calcium (75-85%) | Uric Acid (5-10%) | Struvite (5-10%) | Cystine (1%) |
|---|---|---|---|---|
| **Etiology** | Hypercalciuria<br>Hyperuricosuria (25% of patients with $Ca^{2+}$ stones)<br>Hyperoxaluria (<5% of patients)<br>Hypocitraturia (12% of patients)<br>Other causes:<br>Hypomagnesemia – associated with hyperoxaluria and hypocitraturia<br>High dietary $Na^+$<br>Decreased urinary proteins<br>High urinary pH, low urine volume (e.g. GI water loss)<br>Hyperparathyroidism, obesity, gout, DM | Uric acid precipitates in low volume, acidic urine with a high uric acid concentration:<br>Hyperuricosuria alone<br>Drugs (ASA, thiazides)<br>Diet (purine rich red meats)<br>Hyperuricosuria with hyperuricemia<br>Gout<br>High rate of cell turnover or cell death (leukemia, cytotoxic drugs) | Infection with urea-splitting organisms (*Proteus, Pseudomonas, Providencia, Klebsiella, Mycoplasma, Serratia, S. aureus*) results in alkaline urinary pH and precipitation of struvite (magnesium ammonium phosphate) | Autosomal recessive defect in small bowel mucosal absorption and renal tubular absorption of dibasic amino acids results in "COLA" in urine (cystine, ornithine, lysine, arginine) |
| **Key Features** | Radiopaque on KUB<br>Reducing dietary $Ca^{2+}$ is NOT an effective method of prevention/treatment | Radiolucent on KUB<br>Radiopaque on CT<br>Acidic urine, pH <5.5 (NOT necessarily elevated urinary uric acid) | Perpetuates UTI because stone itself harbours organism<br>Stone and all foreign bodies must be cleared to avoid recurrence<br>Associated with staghorn calculi<br>Positive urine dip and cultures<br>Note: *E. coli* infection does not cause struvite stones<br>M:F = 3:1, UTI more common in female | Aggressive stone disease seen in children and young adults<br>Recurrent stone formation, family Hx<br>Often staghorn calculi<br>Faintly radiopaque on KUB<br>Positive urine sodium nitroprusside test, urine chromatography for cystine |
| **Treatment**<br>Medical if stone <5 mm and no complications<br><br>Procedural/Surgical treatment if stone >5 mm or presence of complications<br><br>Can observe selected, asymptomatic stones | Fluids to increase urine volume to >2 L/d<br>For calcium stones: increase citrate in diet, reduce salt, moderate oxalate-rich foods, weight loss<br>Calcium oxalate: thiazides, ± potassium citrate, ± allopurinol<br>Calcium struvite: ABx (stone must be removed to treat infection) | Increased fluid intake<br>Alkalinization of urine to pH 6.5 to 7 (potassium citrate, sodium bicarbonate)<br>± allopurinol | Complete stone clearance<br>ABx for 6 wk<br>Regular follow-up urine cultures | Increased fluid intake (3-4 L of urine/d)<br>Alkalinize urine (bicarbonate, potassium citrate), Penicillamine/α-MPG or Captopril (form complex with cystine)<br>ESWL not effective |

# Urological Neoplasms

## Approach to Renal Mass

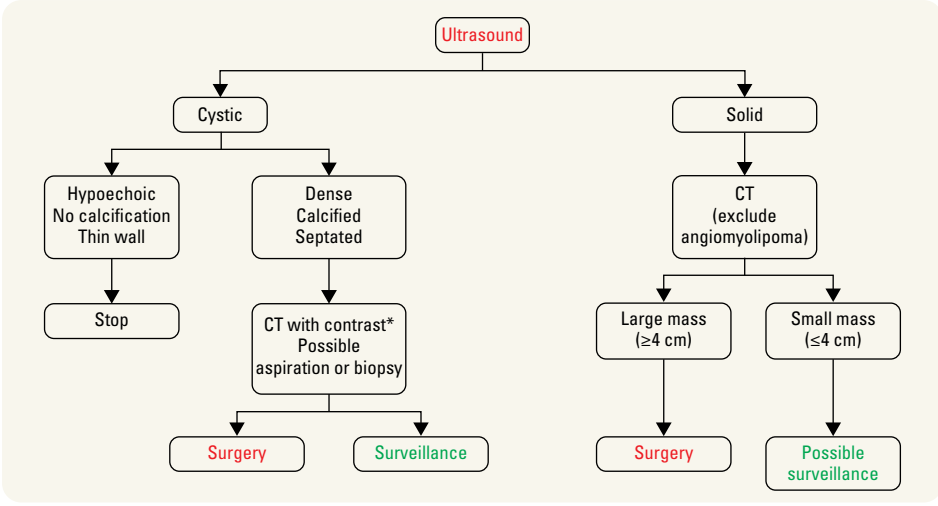



**Figure 13. Workup of a renal mass**
*Imaging modality may be different in cases of contrast allergy or elevated creatinine

There is controversy over optimal management of small renal masses

Percutaneous needle biopsies of cystic renal masses may lead to peritoneal seeding

**Tuberous Sclerosis**
- Syndrome characterized by mental retardation, epilepsy, and adenoma sebaceum
- 45-80% of patients also present with angiomyolipomas which are often multiple and bilateral

## Benign Renal Neoplasms

### CYSTIC KIDNEY DISEASE

- simple cysts: usually solitary or unilateral
  - very common: up to 50% at age 50
  - usually incidental finding on abdominal imaging
  - Bosniak Classification is used to stratify for risk of malignancy based on cyst features from contrast CT
- polycystic kidney disease
  - autosomal recessive: multiple bilateral cysts, often leading to early renal failure in infants
  - autosomal dominant: progressive bilateral disease leading to HTN and renal failure, adult-onset
- medullary sponge kidney: cystic dilatation of the collecting ducts
  - usually benign course, but patients are predisposed to stone disease
- von Hippel-Lindau syndrome: multiple bilateral cysts or renal cell carcinomas (50% incidence of RCC)
  - renal cysts, cerebellar, spinal and retinal hemangioblastomas, pancreatic and epididymal cysts, pheochromocytomas

**Table 14. Bosniak Classification of Renal Cysts**

| Class | Features | Risk of Malignancy | Management Plan |
|---|---|---|---|
| **I (simple cyst)** | Round, no septa/ calcifications/enhancement, homogeneous, <20 HU | Near zero | No follow-up |
| **II (simple cyst)** | Thin septum (<1 mm), fine calcification, no enhancement, <3 cm, >20 HU | Minimal | No follow-up |
| **IIF (minimally complex cyst)** | Multiple thin septa, calcifications, no enhancement, >3 cm, >20 HU | 5-20% | Follow-up, imaging q6-12mo, surgical resection if lesion evolves |
| **III (complex cyst)** | Irregular, thickened, calcified septa with enhancement | >50% | Surgical resection |
| **IV (likely malignant)** | Irregular, thickened, calcified septa with enhancement, enhancing soft-tissue components | >90% | Surgical resection |

**Table 15. Benign Renal Masses**

| | Angiomyolipoma (Renal Hamartoma) | Renal Oncocytoma |
|---|---|---|
| **Epidemiology** | <10% of adult renal tumours<br>F>M<br>20% associated with tuberous sclerosis (especially if multiple, recurrent) | 3-7% of renal tumours<br>M>F<br>Oncocytomas also found in adrenal, thyroid and parathyroid glands |
| **Characteristics** | Clonal neoplasm consisting of blood vessels (angio-), smooth muscle (-myo-), and fat (-lipoma)<br>May extend into regional lymphatics and other organs and become symptomatic | Spherical, capsulated with possible central scar<br>Histologically organized aggregates of eosinophilic cells originating from intercalated cells of collecting duct |
| **Diagnosis** | Incidental finding on CT<br>Negative attenuation (-20 HU) on CT is pathognomonic<br>Rare presentation of hematuria, flank pain, and palpable mass (same as RCC) | Incidental finding on CT<br>Difficult to distinguish from RCC on imaging – treated as RCC until proven otherwise<br>Biopsy may be performed to rule out malignancy |
| **Management** | May consider surgical excision or embolization if symptomatic (pain, bleeding) or higher risk of bleeding (e.g. pregnancy)<br>Potential role for mTOR inhibitors in unresectable/metastatic disease<br>Follow with serial U/S | Partial/radical nephrectomy for large masses<br>HIFU or RFA for smaller masses |

# Malignant Renal Neoplasms

## RENAL CELL CARCINOMA

### Etiology
- cause unknown
- originates from proximal convoluted tubule epithelial cells in clear cell subtype (most common)
- hereditary forms seen with von Hippel-Lindau syndrome and hereditary papillary renal carcinoma

### Epidemiology
- 85% of primary malignant tumours in kidney, ~3% of all malignancies
- M:F = 1.5:1
- peak incidence at 50-60 yr of age

### Pathology
- histological subtypes: clear cell (75-85%), papillary (10-15%), chromophobe (5-10%), collecting duct (<1%), other (<1%)
- sarcomatoid elements in any subtype is a marker of poor prognosis

### Risk Factors
- top 3 risk factors: smoking, HTN, obesity
- end-stage renal disease
- miscellaneous: horseshoe kidney, acquired renal cystic disease
- role of environmental exposures (aromatic hydrocarbons, etc.) remains an unproven risk factor for development of RCC

### Clinical Features
- usually asymptomatic: frequently diagnosed incidentally by U/S or CT (>50%)
- indicators for poor prognosis: weight loss, weakness, anemia, bone pain
- classic "too late triad" found in 10-15%
  - gross hematuria 50%
  - flank pain <50%
  - palpable mass <30%
- metastases: seen in a 1/3 of new cases; additional 20-40% will go on to develop metastases (mostly in late presentations or large tumours)
  - bone, brain, lung and liver most common site
  - may invade renal veins and IVC lumen. This may result in ascites, hepatic dysfunction, right atrial tumour, and pulmonary emboli

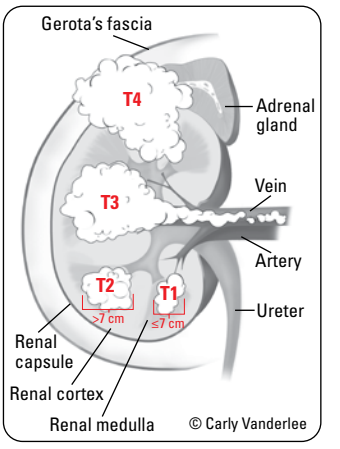



**Figure 14. RCC staging**

Role of environmental exposures (aromatic hydrocarbons, etc.) remains an unproven risk factor for development of RCC

**RCC Systemic Effects: paraneoplastic syndromes (10-40% of patients)**
- Hematopoietic disturbances: anemia, polycythemia, raised ESR
- Endocrinopathies: hypercalcemia (increased vitamin D hydroxylation), erythrocytosis (increased erythropoietin), HTN (increased renin), production of other hormones (prolactin, gonadotropins, TSH, insulin, and cortisol)
- Hepatic cell dysfunction or Stauffer syndrome: abnormal LFTs, decreased WBC count, fever, areas of hepatic necrosis; no evidence of metastases; reversible following removal of primary tumour
- Hemodynamic alterations: systolic HTN (due to AV shunting), peripheral edema (due to caval obstruction)

Tumour may invade renal veins and inferior vena cava lumen. This may result in ascites, hepatic dysfunction, right atrial tumour, and pulmonary emboli

## Investigations
- routine labs for paraneoplastic syndromes (CBC, ESR, LFTs, extended electrolytes)
- U/A
- renal U/S: solid vs. cystic lesion
- contrast-enhanced CT: higher sensitivity than U/S for detection of renal masses and for staging purposes
- MRI: useful for evaluation of vascular extension
- renal biopsy: to confirm diagnosis if considering observation or other non-surgical therapy
- genetic testing: consider if FHx of von Hippel-Lindau syndrome, non-clear cell carcinoma, bilateral/multifocal tumour, onset ≤45 yr, FHx of renal tumour, or any renal tumour with Hx of pneumothorax, dermatologic findings, associated tumours, lymphangiomyomatosis, or childhood seizure disorder

## Staging
- involves CT, CXR, liver enzymes and LFTs, bone/head imaging (if symptoms dictate)

**Table 16. 2018 TNM Classification of Renal Cell Carcinoma (AJCC 8th edition)**

| T | N | M |
|---|---|---|
| **TX**: primary tumour cannot be assessed<br><br>**T1**: tumour <7 cm, confined to renal parenchyma<br>**T1a**: <4 cm<br>**T1b**: 4-7 cm<br><br>**T2**: tumour >7 cm, confined to renal parenchyma<br>**T2a**: >7 cm but ≤10 cm<br>**T2b**: >10 cm<br><br>**T3**: tumour extends into major veins or perinephric tissues, but NOT into ipsilateral adrenal or beyond Gerota's fascia<br>**T3a**: into renal vein or sinus fat<br>**T3b**: into infradiaphragmatic IVC<br>**T3c**: into supradiaphragmatic IVC<br><br>**T4**: tumour extends beyond Gerota's fascia including extension into ipsilateral adrenal<br><br>**T Suffix**<br>**(m):** if synchronous primary tumours are found in single organ | **NX:** regional lymph nodes cannot be assessed<br><br>**N0**: no regional lymph node metastasis<br><br>**N1**: metastasis in regional lymph nodes<br><br>**N Suffix**<br>**(sn):** regional lymph node metastasis identified by SLN biopsy only<br>**(f):** regional lymph node metastasis identified by FNA or core needle biopsy only | **cM0**: no evidence of distance metastasis<br><br>**cM1**: presence of distance metastasis<br><br>**pM1**: presence of distant metastasis, microscopically confirmed |



**Differential Diagnosis of Filling Defect**
- Urothelial carcinoma (differentiate via cytology and CT scan)
- Uric acid stone (differentiate via cytology and CT scan)
- Blood clot
- Pyelitis cystica
- Papillary necrosis
- Fungus ball
- Gas bubble from gas producing organisms

## Treatment
- surgical (open, laparoscopic, robotic)
  - radical nephrectomy: en bloc removal of kidney, tumour, ipsilateral adrenal gland (in upper pole tumours) and intact Gerota's capsule
  - partial nephrectomy (parenchyma-sparing): small tumour (roughly <4 cm) or solitary kidney/bilateral tumours
  - surgical removal of solitary metastasis may be considered
- ablative techniques (RFA)
- palliative radiation to painful bony lesions
- therapy for advanced stage
  - tyrosine kinase inhibitors for metastatic disease (e.g. sunitinib, sorafenib)
  - anti-angiogenesis/anti-VEGF (e.g. bevacizumab)
  - mTOR inhibitors (e.g. temsirolimus, everolimus)
  - high-dose IL-2 (high toxicity but able to induce long-term cure in 5-7% of patients)
  - IFN-α: monotherapy has been largely replaced by molecularly targeted agents listed above

## Prognosis
- stage at diagnosis most important prognostic factor
  - T1: 90-100% 5 yr survival
  - T2-T3: 60% 5 yr survival
  - metastatic disease: <5% 10 yr survival
- predictors of relapse: tumour grade, local extent of the primary tumour, presence of local metastases, histological subtype

# Carcinoma of the Renal Pelvis and Ureter

### Etiology
- risk factors include:
  - smoking
  - chemicals/dietary exposures (industrial dyes and solvents; aristolochic acid, aniline dyes)
  - analgesic abuse (acetaminophen, ASA, and phenacetin)
  - Balkan nephropathy
  - prior exposure to cyclophosphamide

### Epidemiology
- rare: accounts for 5% of all urothelial cancers
- frequently multifocal, 2-5% are bilateral
- M:F = 3:1
- relative incidence: bladder:renal:ureter = 100:10:1

### Pathology
- 85% are papillary urothelial carcinoma; others include SCC and adenocarcinoma
- UC of ureter and renal pelvis are histologically similar to bladder UC

### Clinical Features
- gross/microscopic hematuria
- flank pain
- storage or voiding symptoms (dysuria only if lower urinary tract involved)
- flank mass ± hydronephrosis (10-20%)

### Investigations
- CT urogram
- cystoscopy and retrograde pyelogram

### Treatment
- radical nephroureterectomy with excision of ipsilateral bladder cuff
- distal ureterectomy for distal ureteral tumours with concomitant ureteral reimplant
- segmental resection with uretero-ureterostomy for some mid-ureteral tumours is also done
- emerging role for endoscopic laser ablation in patients with low grade disease, poor baseline renal health

# Bladder Carcinoma

### Etiology
- unknown, but environmental risk factors include:
  - smoking (main factor – implicated in 60% of new cases)
  - aromatic amines: naphthylamines, benzidine, tryptophan, phenacetin metabolites
  - cyclophosphamide
  - prior Hx of radiation treatment to the pelvis
  - *Schistosoma hematobium* infection (associated with SCC)
  - chronic irritation: cystitis, chronic catheterization, bladder stones (associated with SCC)
  - aristolochic acid: associated with Balkan Nephropathy (renal failure, upper tract urothelial cancer) and Chinese Herbal Nephropathy

### Epidemiology
- 2nd most common urological malignancy
- M:F = 3:1, more common among whites than blacks
- mean age at diagnosis is 65 yr

### Pathology
- classification
  - urothelial carcinoma (UC) >90%
  - SCC 5-7%
  - adenocarcinoma 1%
  - others <1%
- stages and prognoses of urothelial carcinoma at diagnosis
  - non-muscle invasive (75%) → >80% overall survival
    - 15% of these will progress to invasive UC
    - majority of these patients will have recurrence
  - invasive (25%) → 50-60% 5 yr survival
    - 85% have no prior history of superficial UC (i.e. de novo)
    - 50% have occult metastases at diagnosis, and most of these will develop overt clinical evidence of metastases within 1 yr – lymph nodes, lung, peritoneum, liver
- carcinoma *in situ* → flat, non-papillary erythematous lesion characterized by dysplasia confined to urothelium
  - more aggressive, worse prognosis
  - usually multifocal
  - may progress to invasive UC

**Radiotherapy With or Without Chemotherapy in Muscle-Invasive Bladder Cancer**
NEJM 2012;366:1477-1488
**Study**: Phase 3 trial with random assignment of 360 patients with muscle-invasive bladder cancer to radiotherapy with or without chemotherapy.
**Results**: At 2 yr, rates of locoregional disease-free survival were 67% in the chemoradiotherapy group and 54% in the radiotherapy group (HR 0.68, 95% CI 0.48-0.96). Five year overall survival rates were 48% in the chemoradiotherapy group and 35% in the radiotherapy group (HR 0.82, 95% CI 0.63-1.09).
**Conclusions**: Chemotherapy with fluorouracil and mitomycin C in combination with radiotherapy improves locoregional control of bladder cancer compared to radiotherapy alone, with no significant increase in adverse events.

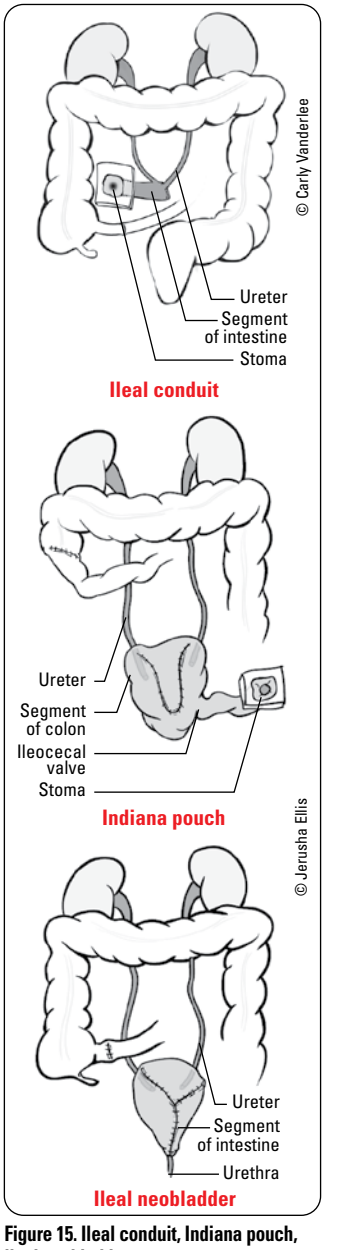



**Figure 15. Ileal conduit, Indiana pouch, ileal neobladder**

## Clinical Features
- asymptomatic (20%)
- hematuria (key symptom: 85-90% at the time of diagnosis)
- pain (50%) → location determined by size/extent of tumour (i.e. flank, suprapubic, perineal, abdominal, etc.)
- clot retention (17%)
- storage urinary symptoms → consider carcinoma in situ
- palpable mass on bimanual exam → likely muscle invasion
- obstruction of ureters → hydronephrosis and uremia (nausea, vomiting, and diarrhea)

## Investigations
- U/A, urine C&S, urine cytology
- U/S
- CT scan with contrast → look for filling defects in upper tracts
- cystoscopy with biopsy (if small lesion)
- TURBT (gold standard, diagnostic and often therapeutic) → establish diagnosis and determine depth of penetration
- specific bladder tumour markers (e.g. NMP-22, BTA, Immunocyt, FDP); utility in clinical practice debatable

## Grading
- low grade: ≤10% invasive, 60% recur locally
- high grade: 50-80% are invasive or are expected to progress to invasive over time

## Staging
- for invasive disease: CT or MRI, CXR, LFTs, extended electrolytes ($Ca^{2+}$, $Mg^{2+}$, $PO_4^{3-}$) (metastatic workup)

**Table 17. 2018 TNM Classification of Bladder Carcinoma (AJCC 8th edition)**

| T | N | M |
|---|---|---|
| **TX**: Primary tumour cannot be assessed<br>**T0**: No evidence of primary tumour<br>**Ta**: Noninvasive papillary carcinoma<br>**Tis**: Carcinoma *in situ*: "flat tumour"<br>**T1**: Tumour invades subepithelial connective tissue<br>**T2**: Tumour invades muscularis propria<br>**pT2a**: Tumour invades superficial muscularis propria (inner half)<br>**pT2b**: Tumour invades deep muscularis propria (outer half)<br>**T3**: Tumour invades perivesical tissue<br>**pT3a**: Microscopically<br>**pT3b**: Macroscopically (extravesical mass)<br>**T4**: Tumour invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall<br>**T4a**: Tumour invades prostatic stroma, uterus, vagina<br>**T4b**: Tumour invades pelvic wall, abdominal wall<br>**T Suffix**<br>**(m):** Synchronous primary tumours are found in single organ | **NX**: Lymph nodes cannot be assessed<br>**N0**: No lymph node metastasis<br>**N1**: Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)<br>**N2**: Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis)<br>**N3**: Lymph node metastasis to the common iliac lymph nodes<br>**N Suffix**<br>**(sn):** regional lymph node metastasis identified by SLN biopsy only<br>**(f):** regional lymph node metastasis identified by FNA or core needle biopsy only | **cM0:** No distant metastasis<br>**cM1:** Distant metastasis<br>**cM1a:** Distant metastasis limited to lymph nodes beyond the common iliacs<br>**cM1b:** Non-lymph-node distant metastasis<br>**pM1:** Distant metastasis, microscopically confirmed<br>**pM1a:** Distant metastasis limited to lymph nodes beyond the common iliacs , microscopically confirmed<br>**pM1b:** Non-lymph-node distant metastasis microscopically confirmed |

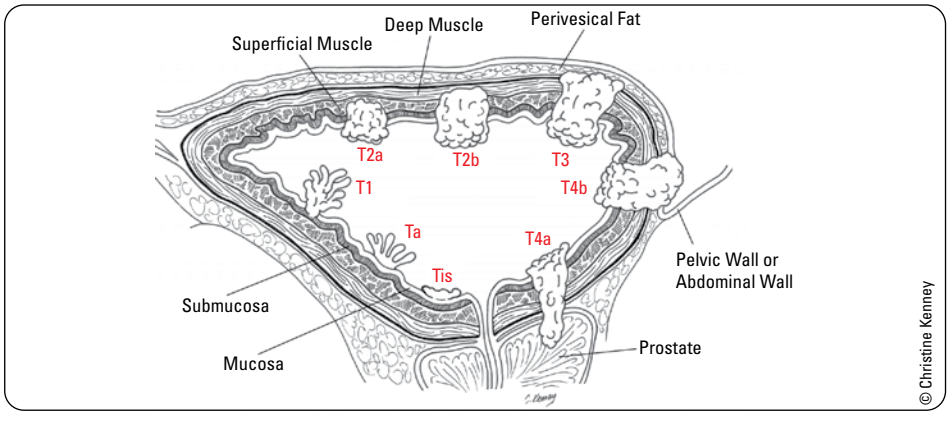



**Figure 16. Urothelial carcinoma of bladder**

The "field defect" theory helps to explain why UC has multiple lesions and has a high recurrence rate. The entire urothelium (pelvis to bladder) is bathed in carcinogens

The ENTIRE urinary tract must be evaluated in patients with hematuria unless there is clear evidence of glomerular bleeding (e.g. red cell casts, dysmorphic RBCs, etc.)

Cystoscopy is the initial procedure of choice for the diagnosis and staging of urothelial malignancy

Unexplained hematuria in any individual >40 yr old must be investigated to rule out a malignancy

Tumour grade is the single most important prognostic factor for progression

**Neoadjuvant Chemotherapy plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer**
NEJM 2003;349:859-866
**Study**: Randomized clinical trial.
**Patients**: 317 patients with transitional-cell carcinoma of the bladder (T2N0M0 to T4aN0M0).
**Intervention**: Randomized to undergo radical cystectomy or to receive three cycles of combined chemotherapy (methotrexate, vinblastine, doxorubicin, and cisplatin) followed by radical cystectomy.
**Main Outcome**: Survival. Secondary objective was to quantify down-staging of tumour following chemotherapy.
**Results**: At 5 yr after treatment initiation, 57% of the combination-therapy group vs. 43% of the cystectomy group were alive (p=0.06). In the combination-therapy group, 38% of the patients were pathologically free of cancer at the time of cystectomy vs. 15% of the cystectomy-only group at the time of surgery (p<0.001).
**Conclusions**: For locally advanced bladder carcinoma, neoadjuvant chemotherapy significantly reduces tumour volume and also improves survival.

**Non-Muscle-Invasive Bladder Cancer (NMIBC) and BCG**
AHRQ Publication 2015:15-EHC017-EF #153
**Summary**: BCG is the only intravesical therapy associated with decreased risk of bladder cancer progression; however, it is also associated with a high rate of adverse events. More research is needed to define optimal dose/regimen.
**Methods**: Review of Ovid Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of SR, Health Technology Assessment, National Health Sciences Economic Evaluation, Database of Abstract of Review of Effects for studies on NMIBC interventions, including intravesical therapy.
**Results**: BCG is superior in prevention of bladder cancer recurrence compared to no intravesical therapy. BCG is superior to doxorubicin, epirubicin, and mitomycin in prevention of bladder cancer recurrence.

### Treatment

| Non-muscle invasive | Muscle invasive | Advanced/Metastatic |
|---|---|---|
| **Low risk (Ta low-grade)**<br>TURBT + intravesical chemo<br>Follow-up with cystoscopy and cytology<br><br>**Intermediate risk (Multifocal, recurrent Ta)**<br>TURBT + intravesical chemo<br>BCG (1 yr)<br><br>**High risk (T1, Tis, Ta high-grade)**<br>TURBT ± intravesical chemo<br>Repeat TURBT (2-6 wk)<br>BCG (3 yr) | **T2, T3**<br>Radical cystectomy + PLND + urinary diversion (see Figure 15)<br>Neoadjuvant chemo<br>Maximal TURBT + chemoradiation | **T4, N+, M+**<br>Chemo ± radiation ± cystectomy |

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**Figure 17. Treatment for bladder carcinoma**

### Prognosis
- depends on stage, grade, size, number of lesions, recurrence and presence of CIS
  - T1: 90% 5 yr survival
  - T2: 55% 5 yr survival
  - T3: 30% 5 yr survival
  - T4/N+/M+: <5% 5 yr survival

**10 Year Outcomes After Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer**
*NEJM.* 2016;375(15):1415-1424
**Summary**: At 10 years, prostate-cancer-specific mortality was low regardless of the treatment, with no significant difference among treatments. Surgery and radiotherapy were associated with lower incidences of disease progression and metastasis vs. active monitoring.
**Methods**: 1643 men randomized into active monitoring (545), surgery (553), and radiotherapy (545).
- Primary outcome: prostate-cancer mortality at median 10 year follow-up.
- Secondary outcomes: rate of disease progression, metastases, and all-cause deaths.

**Results**:
1. Primary outcome: 17 prostate-cancer-specific deaths overall; 8 in active-monitoring group, 5 in the surgery group, and 4 in the radiotherapy group; difference among the groups was not significant (p=0.48). No significant difference was seen among groups in numbers of deaths from any cause (169 deaths overall; p=0.87).
2. Secondary outcomes: metastases developed more in active monitoring group (33 men) vs. surgery group (13 men) or radiotherapy group (16 men) (overall p=0.004). Higher rates of disease progression in active-monitoring group (112 events) vs. surgery group (46 events) or radiotherapy group (46 events) (p<0.001 for the overall comparison).

# Prostate Cancer

### Etiology
- not known
- risk factors
  - age >50 yr, risk increases 1% per year after 65 yr
  - increased incidence in persons of African descent
  - high dietary fat (2x)
  - family Hx
    - 1st degree relative (2x)
    - 1st and 2nd degree relatives (9x)
  - positive BRCA mutation

### Epidemiology
- most prevalent cancer in males
- 3rd leading cause of male cancer deaths (following lung and colon)
- up to 50% risk of CaP at age 50
- lifetime risk of death from CaP is 3%
- 75% diagnosed between ages of 60 and 85; mean age at diagnosis is 65

### Pathology
- adenocarcinoma
  - >95%, often multifocal
- urothelial carcinoma of the prostate (4.5%)
  - associated with UC of bladder; does NOT follow TNM staging below; not hormone-responsive
- endometrial (rare)
  - carcinoma of the utricle

### Anatomy
- 60-70% of nodules arise in the peripheral zone
- 10-20% arise in the transition zone
- 5-10% arise in the central zone

### Clinical Features
- usually asymptomatic
- most commonly detected by DRE, elevated PSA, or as an incidental finding on TURP
  - DRE: hard irregular nodule or diffuse dense induration involving one or both lobes
  - PSA: see *PSA Screening*, U28
- locally advanced disease
  - storage and voiding symptoms, ED (all uncommon without spread)
- metastatic disease
  - bony metastases to axial skeleton common
  - visceral metastases are less common (liver, lung, and adrenal gland most common sites)
  - leg pain and edema with nodal metastases obstructing lymphatic and venous drainage

## Methods of Spread
- local invasion
- lymphatic spread to regional nodes
  - obturator > iliac > presacral/para-aortic
- hematogenous dissemination occurs early

## Investigations
- DRE
- PSA elevated in the majority of patients with CaP
- TRUS-guided needle biopsy
- bone scan (only if bone pain, high risk disease, or PSA >20 ng/mL)
- CT scanning to assess metastases
- MRI: being investigated for possible role in detection, staging, MRI-guided biopsy and active surveillance

**Table 18. 2018 TNM Classification of Prostate Carcinoma (AJCC 8th edition)**

| T | N | M |
|---|---|---|
| **TX:** Primary tumour cannot be assessed<br><br>**T0:** No evidence of primary tumour<br><br>**T1**: clinically undetectable tumour, normal DRE and TRUS<br>**T1a**: tumour incidental histologic finding in <5% of tissue resected<br>**T1b**: tumour incidental histologic finding in >5% of tissue resected<br>**T1c**: tumour identified by needle biopsy (due to elevated PSA level)<br><br>**T2**: palpable, confined to prostate<br>**T2a**: tumour involving ≤ one half of one lobe<br>**T2b**: tumour involving > one half of one lobe, but not both lobes<br>**T2c**: tumour involving both lobes<br><br>**T3**: tumour extends through prostate capsule<br>**T3a**: extracapsular extension (unilateral or bilateral)<br>**T3b**: tumour invading seminal vesicle(s)<br><br>**T4**: tumour invades adjacent structures (besides seminal vesicles)<br><br>**T Prefix**<br>**(c):** Clinical T<br>**(p):** Pathological T. There is no pathological T1<br><br>**T Suffix**<br>**(m):** Synchronous primary tumours are found in single organ | **NX**: regional lymph nodes were not assessed<br><br>**N0**: no regional lymph node metastasis<br><br>**N1**: spread to regional lymph nodes<br><br>**N Suffix**<br>**(sn):** regional lymph node metastasis identified by SLN biopsy only<br>**(f):** regional lymph node metastasis identified by FNA or core needle biopsy only | **M0:** no distant metastasis<br><br>**cM1:** distant metastasis<br>**cM1a:** nonregional lymph nodes<br>**cM1b:** bone(s)<br>**cM1c:** other site(s) with or without bone disease<br><br>**pM1:** distant metastasis, microscopically confirmed<br>**pM1a:** nonregional lymph nodes, microscopically confirmed<br>**pM1b:** bone(s). microscopically confirmed<br>**pM1c:** other site(s) with or without bone disease, microscopically confirmed |

**Table 19. Prostate Cancer Mortality Risk**

| | Low Risk (if any of following) | Intermediate Risk (if any of following) | High Risk (if any of following) |
|---|---|---|---|
| **PSA** | <10 | 10-20 | >20 |
| **Gleason Score** | <7 | 7 | 8-10 |
| **Stage** | pT1-2a | pT2b-T2c | pT3/4 |

## Treatment
- T1/T2 (localized, low-risk)
  - if adequate life expectancy or no other significant comorbidities, consider active surveillance vs. definitive local treatment (RP, brachytherapy, or EBRT)
  - active surveillance for low risk, small volume Gleason 6 prostate cancer shown to be safe for most
  - minimal differences in cure or recurrence rates between definitive treatment modalities
  - in older population: watchful waiting + palliative treatment for symptomatic progression
- T1/T2 (intermediate or high-risk)
  - definitive therapy over active surveillance
  - watchful waiting in elderly or infirm
- T3, T4
  - EBRT + androgen deprivation therapy
  - RP + adjuvant EBRT
- N >0 or M >0
  - requires hormonal therapy/palliative radiotherapy for metastases; may consider combined androgen blockade
  - bilateral orchiectomy – decreases testosterone production by 90%
  - GnRH agonists (e.g. leuprolide, goserelin), see Table 28, GnRH antagonist (e.g. degarelix)
  - antiandrogens (e.g. bicalutamide)
  - local irradiation of painful secondaries or half-body irradiation



**Screening for Prostate Cancer**
Cochrane DB Syst Rev 2013;1:CD004720
**Background**: Screening for prostate cancer has an unclear benefit for reducing prostate cancer-specific mortality and morbidity.
**Study**: Systematic review of randomized clinical trials of screening vs. no screening. A total of 31 trials were retrieved for this review.
**Results**: A meta-analysis of 5 RCTs with 341,342 participants was done. Collectively, there was no significant reduction in prostate cancer-specific mortality within 10 yr of follow-up. Screening procedures and biopsies were commonly associated with bleeding, bruising, and short-term anxiety; subsequent over-diagnosis and overtreatment resulted in additional harms, some severe.
**Conclusions**: Men who have a life expectancy less than 10-15 yr should be informed that screening for prostate cancer is unlikely to be beneficial. Significant harms are associated with screening, over-diagnosis, and overtreatment.

- hormone-refractory prostate cancer
  - chemotherapy: docetaxel, cabazitaxel
  - novel antiandrogens (e.g. abiraterone, enzalutamide)
  - other novel agents: denosumab, sipuleucel-T

**Table 20. Treatment Options for Localized Prostate Cancer**

| Modality | Population Considered | Limitations |
|---|---|---|
| **Watchful Waiting** | Short life expectancy (<5-10 yr); will likely only receive non-curative hormonal therapy if disease progresses | Disease progression |
| **Active Surveillance (serial PSA, DRE, and biopsies)** | Low grade disease, good follow-up; is still considering more curative treatment if disease progresses | Disease progression; decrease in QOL associated with serial testing; risks associated with biopsies; no optimal monitoring schedule has been defined to date |
| **Brachytherapy** | Low volume, low PSA (<10), low grade | ED (50%), long-term effectiveness not well-established |
| **EBRT** | Locally advanced disease, older patients | Radiation proctitis (5%), ED (50%), risk of rectal cancer |
| **RP** | Young patients (<75 yr), high-risk disease | Incontinence (10%), ED (30-50%) |

*Other options include cryosurgery, HIFU, hormonal ablation

### Prognosis
- T1-T2: comparable to normal life expectancy
- T3-T4: 40-70% 10 yr survival
- $N^+$ and/or $M^+$: 4% 5 yr survival
- prognostic factors: tumour stage, tumour grade, PSA value, PSA doubling time

## PSA Screening

### Digital Rectal Exam
- should be included as part of initial screening
- suspicious findings: abnormal feeling, nodularity, focal lesion, discrete change in texture/fullness/symmetry

### Prostate Specific Antigen
- glycoprotein produced by epithelial cells of prostate gland
- leaks into circulation in setting of disrupted glandular architecture
- value of <4 ng/mL traditionally considered as cut-off to differentiate normal from pathologic value, but no single justifiable cut-off point
- measured serum PSA is a combination of free (15%) and bound PSA (85%)
- decreased free:total PSA, elevated PSA velocity and elevated PSA density associated with increased CaP rates

### Screening Recommendations

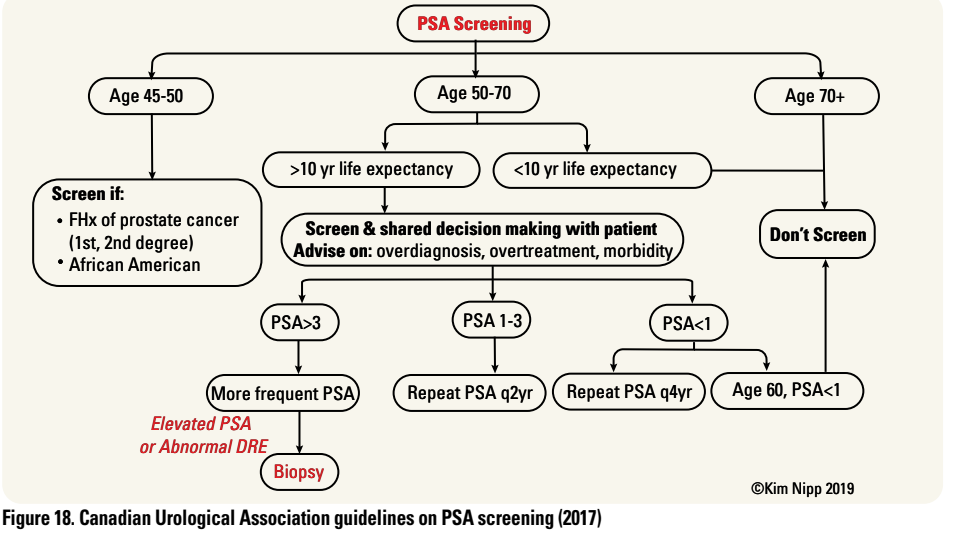



**Figure 18. Canadian Urological Association guidelines on PSA screening (2017)**

**Causes of Increased PSA**
BPH, prostatitis, prostatic ischemia/infarction, prostate biopsy/surgery, prostatic massage, acute urinary retention, urethral catheterization, cystoscopy, TRUS, strenuous exercise, perineal trauma, ejaculation, acute renal failure, coronary bypass graft, radiation therapy

PSA is specific to the PROSTATE, but NOT to prostate cancer

**Long-Term Follow-Up on PSA Screening**
Lancet 2014;384:2027-2035
**Summary**: With 13 yr follow-up, the mortality reduction remains unchanged (21%, and 29% after non-compliance adjustment). However, the number needed to screen and to treat is decreasing, and is now below the number needed to screen observed in breast cancer trials.
**Methods**: multi-centre RCT with predefined central database, analysis, and core age group (55-69 years) evaluating PSA in 8 European countries. Incidence and mortality truncated at 9, 11, and 13 years follow-up in the intervention arm was compared to control arm.
**Results**: RR of PCa incidence between intervention and control arms was 1.91 after 9 yr follow-up, 1.66 at 11 year follow-up, and 1.67 at 13 yr follow-up. RR of PCa mortality was 0.85, 0.78, and 0.79, at 9, 11, 13 yr follow-up, respectively. RRR is 21%, and ARR from death is 1.28 per 1000 men.

# Testicular Tumours

## Etiology/Risk Factors
- cryptorchidism, atrophy, sex hormones, HIV infection, infertility, family Hx, past Hx of testicular cancer

## Epidemiology
- rare, but most common solid malignancy in young males 15-35 yr
- any solid testicular mass or acute hydrocoele in young patient – must rule out malignancy
- slightly more common in right testis (corresponds with slightly higher incidence of right-sided cryptorchidism)
- 2-3% bilateral (simultaneously or successively)

## Pathology
- primary
  - 1% of all malignancies in males
  - cryptorchidism has increased risk (10-40x) of malignancy
  - 95% are germ cell tumours (all are malignant)
    - seminoma (35%) → classic, anaplastic, spermatocytic
    - NSGCT → embryonal cell carcinoma (20%), teratoma (5%), choriocarcinoma (<1%), yolk sac (<<1%), mixed cell type (40%)
  - 5% are non-germ cell tumours (usually benign) → Leydig (testosterone, precocious puberty), Sertoli (gynecomastia, decreased libido)
- secondary
  - male >50 yr
  - usually lymphoma or metastases (e.g. lung, prostate, GI)

## Clinical Features
- painless testicular enlargement (painful if intratesticular hemorrhage or infarction)
- dull, heavy ache in lower abdomen, anal area or scrotum
- associated hydrocele (10%)
- coincidental trauma (10%)
- infertility (rarely presenting complaint)
- gynecomastia due to secretory tumour effects
- supraclavicular and inguinal lymphadenopathy
- abdominal mass (retroperitoneal lymph node mets)

## Methods of Spread
- local spread follows lymphatics
  - right → medial, paracaval, anterior, and lateral nodes
  - left → left lateral and anterior paraaortic nodes
  - "cross-over" metastases from right to left are fairly common, but no reports from left to right
- hematogenous most commonly to lung, liver, bones, and kidney



Testes and scrotum have different lymphatic drainage, therefore trans-scrotal approach for biopsy or orchiectomy should be avoided

## Investigations
- diagnosis is established by pathological evaluation of specimen obtained by radical inguinal orchidectomy
- tumour markers (β-hCG, LDH, AFP)
  - β-hCG and AFP are positive in 85% of non-seminomatous tumours
  - elevated marker levels return to normal post-operatively if no metastasis
  - β-hCG positive in 7% of pure seminomas, AFP never elevated with seminoma
- testicular U/S (hypoechoic area within tunica albuginea = high suspicion of testicular cancer)
- evidence of testicular microlithiasis is not a risk factor for testicular cancer
- needle aspiration contraindicated

## Staging
- clinical: CXR (lung mets), markers for staging (β-hCG, AFP, LDH), CT abdomen/pelvis (retroperitoneal lymphadenopathy)
  - Stage I: disease limited to testis, epididymis, or spermatic cord
  - Stage II: disease limited to the retroperitoneal nodes
  - Stage III: disease metastatic to supradiaphragmatic nodal or visceral sites

**Table 21. 2018 TNM Classification of Testicular Carcinoma (AJCC 8th edition)**

| T | N | M |
|---|---|---|
| **TX**: Primary tumour cannot be assessed<br><br>**T0**: No evidence of primary tumour<br><br>**Tis**: intratubular germ cell neoplasia<br><br>**T1**: limited to testis and epididymis without lymphovascular invasion<br>**T1a**: tumour <3 cm<br>**T1b**: tumour >3 cm<br><br>**T2**: limited to testis and epididymis with lymphovascular invasion or invading hilar soft tissue or epididymis, or penetrating visceral mesothelial layer covering the external surface of tunica albuginea with or without lymphovascular invasion<br><br>**T3**: invasion of the spermatic cord ± lymphovascular invasion<br><br>**T4**: invasion of the scrotum ± invasion<br><br>**T Prefix**<br>**(c):** Clinical T. Except for Tis confirmed by biopsy an T4, the extent of primary tumour is classified by radical orchiectomy<br>**(p):** Pathological T. Subclassification of pT1 applies only to pure seminoma<br><br>**T Suffix**<br>**(m):** Synchronous primary tumours are found in single organ | **NX**: regional lymph nodes were not assessed<br><br>**N0**: no regional lymph node metastasis<br><br>**N1**: Metastasis with a lymph node mass 2 cm or less in greatest dimension; or multiple lymph nodes, none more than 2 cm in greatest dimension<br><br>**N2**: Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension<br><br>**N3**: Metastasis with a lymph node mass more than 5 cm in greatest dimension<br><br>**N Prefix**<br>**(c):** Clinical N<br>**(p):** Pathological N<br><br>**N Suffix**<br>**(sn):** regional lymph node metastasis identified by SLN biopsy only<br>**(f):** regional lymph node metastasis identified by FNA or core needle biopsy only | **M0**: no distant mets<br><br>**cM1**: distant mets<br>**cM1a**: non-retroperitoneal nodal or pulmonary mets<br>**cM1b**: non-pulmonary visceral mets<br><br>**pM1**: distant mets, microscopically confirmed<br>**pM1a**: non-retroperitoneal nodal or pulmonary mets, microscopically confirmed<br>**pM1b**: non-pulmonary visceral mets, microscopically confirmed |

## Management
- orchiectomy through inguinal ligament for all stages
- consider sperm banking, testicular prosthesis
- adjuvant therapies (see figure 19)

## Prognosis
- 99% cured with stage I and II disease
- 70-80% complete remission with advanced disease

**Orchiopexy**
Surgical descent (orchiopexy) of undescended testis does not eliminate the risk of malignancy, but allows for earlier detection by self-examination and reduces the risk of infertility

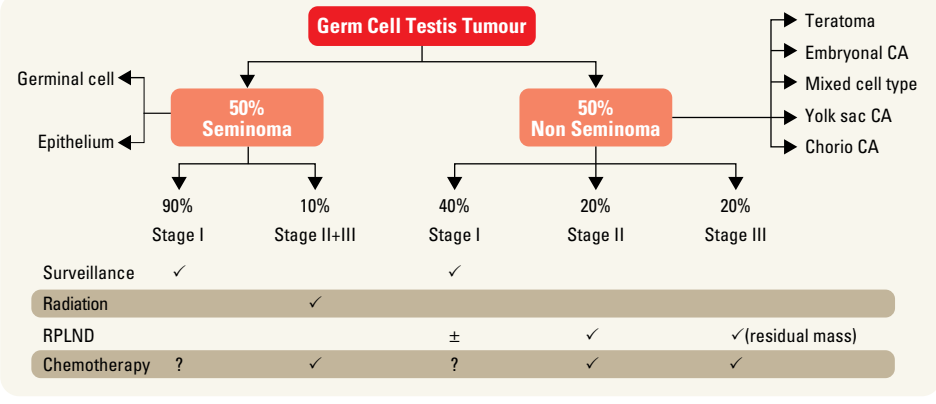



**Figure 19. Adjuvant management of testicular cancer post-orchiectomy** Adapted from Dr. MAS Jewett

# Penile Tumours

## Epidemiology
- rare (<1% of cancer in males in U.S.)
- most common in 6th decade

## Benign
- cyst, hemangioma, nevus, papilloma

## Pre-Malignant
- balanitis xerotica obliterans, leukoplakia, Buschke-Lowenstein tumour (large condyloma)

### Pre-invasive Cancer
- carcinoma *in situ*
  - Bowen's disease → crusted, red plaques on the shaft
  - erythroplasia of Queyrat → velvet red, ulcerated plaques on the glans
  - treatment options: local excision, laser, radiation, topical 5-fluorouracil

### Malignant
- risk factors
  - chronic inflammatory disease
  - STI
  - phimosis
  - uncircumcised penis
- 2% of all urogenital cancers
- SCC (>95%), basal cell, melanoma, Paget's disease of the penis (extremely rare)
- definitive diagnosis requires full thickness biopsy of lesion
- lymphatic spread (superficial/deep inguinal nodes → iliac nodes) >> hematogenous

### Treatment
- wide surgical excision with tumour-free margins (dependent on extent and area of penile involvement) ± lymphadenectomy
- consider less aggressive treatment modalities in CIS (cryotherapy, laser therapy, etc.) if available

# Scrotal Masses

**Table 22. Differentiating between Scrotal Masses**

| Condition | Pain | Palpation | Additional Findings |
|---|---|---|---|
| **Torsion** | + | Diffuse tenderness<br>Horizontal lie of testicle | Absent cremaster reflex, negative Prehn's sign |
| **Epididymitis** | + | Epididymal tenderness | Present cremaster reflex, positive Prehn's sign |
| **Orchitis** | + | Diffuse tenderness | Present cremaster reflex, positive Prehn's sign |
| **Hematocele** | + | Diffuse tenderness | No transillumination |
| **Hydrocele** | – | Testis not separable from hydrocele, cord palpable | Transillumination, Hx of trauma |
| **Spermatocele** | – | Testis separable from spermatocele, cord palpable | Transillumination |
| **Varicocele** | – | Bag of worms | No transillumination, increases in size with valsalva, decrease in size if supine |
| **Indirect Inguinal** | – (+ if strangulated) | Testis separable from hernia, cord not palpable, cough impulse may transmit, may be reducible | No transillumination |
| **Tumour** | – (+ if hemorrhagic) | Hard lump/nodule | |
| **Generalized/ Dependent Edema** | – | Diffuse swelling | Often post-operative or immobilized, check for liver dysfunction |
| **Idiopathic** | – | | |



**Varicocele Grading**
- Grade 1: Palpable only with Valsalva manoeuvre
- Grade 2: Palpable without Valsalva
- Grade 3: Visible through scrotal skin



**Suspect a Retroperitoneal Mass/Process in a Patient with a Varicocele if:**
- Acute onset
- Right sided (isolated)
- Palpable abdominal mass
- Does not reduce while supine



**Indications for Treatment of Varicocele**
- Impaired sperm quality or quantity
- Pain or dull ache affecting QOL
- Affected testis fails to grow in adolescents
- Cosmetic indications (especially in adolescents)

**Table 23. Benign Scrotal Masses**

| Type | Varicocele | Spermatocele | Hydrocele | Testicular Torsion | Inguinal Hernia |
|---|---|---|---|---|---|
| **Definition** | Dilatation and tortuosity of pampiniform plexus | A benign, sperm filled epididymal retention cyst | Collection of serous fluid that results from a defect or irritation in the tunica vaginalis | Twisting of the testicle causing venous occlusion and engorgement as well as arterial ischemia and infarction | Protrusion of abdominal contents through the inguinal canal into the scrotum |
| **Etiology** | 15% of men<br>Due to incompetent valves in the testicular veins<br>90% left sided | Multiple theories, including:<br>Distal obstruction<br>Aneurysmal dilations of the epididymis<br>Agglutinated germ cells | Usually idiopathic<br>Found in 5-10% testicular tumours<br>Associated with trauma/infection<br>Communicating: patent processus vaginalis, changes size during day (peds)<br>Non-communicating: non-patent processus vaginalis (adult) | Trauma<br>Cryptorchidism<br>"Bell clapper deformity"<br>Many occur in sleep (50%)<br>Necrosis of glands in 5-6 h | Indirect (through internal ring, often into scrotum): congenital<br>Direct (through external ring, rarely into scrotum): abdominal muscle weakness |
| **Hx/P/E** | "Bag of worms"<br>Often painless<br>Pulsates with Valsalva | Non-tender, cystic mass<br>Transilluminates | Non-tender, intrascrotal mass<br>Cystic<br>Transilluminates | Acute onset severe scrotal pain, swelling<br>GI upsets cases<br>Retracted and transverse testicle (horizontal lie)<br>Negative Phren's sign<br>Absent cremasteric reflex | A small bulge in the groin that may increase in size with Valsalva and disappear when lying down<br>Can present as a swollen or enlarged scrotum<br>Discomfort or sharp pain – especially when straining, lifting, or exercising |
| **Investigations** | P/E<br>Valsava | P/E<br>U/S to rule out tumour | U/S to rule out tumour | U/S Doppler with probe over testicular artery<br>Decrease uptake on $^{99m}$Tc-pertechnetate scintillation scan (doughnut sign) | Hx and P/E<br>Invagination of the scrotum<br>Valsalva |
| **Treatment** | Conservative<br>Surgical ligation of testicular veins<br>Percutaneous vein occlusion (balloon, sclerosing agents)<br>Repair may improve sperm count/motility 50-75% | Conservative<br>Avoid needle aspiration as it can lead to infection, reaccumulation and spilling of irritating sperm within scrotum<br>Excise if symptomatic | Conservative<br>Needle drainage<br>Surgical | Emergency surgical exploration and bilateral orchiopexy<br>Definitive diagnosis NOT necessary to take to OR<br>Orchiectomy if poor prognosis | Surgical repair |

## TORSION OF TESTICULAR APPENDIX
- twisting of testicular/epididymal vestigial appendix

### Signs and Symptoms
- clinically similar to testicular torsion, but vertical lie and cremaster reflex preserved
- "blue dot sign"
  - blue infarcted appendage seen through scrotal skin in children (can usually be palpated as small, tender lump)

### Treatment
- analgesia – most will subside over 5-7 d
- surgical exploration and excision if refractory pain

## HEMATOCELE
- trauma with bleed into tunica vaginalis
- U/S helpful to exclude fracture of testis which requires surgical repair

### Treatment
- ice packs, analgesics, surgical repair



Acute scrotal swelling/pain in young boys is torsion until proven otherwise



Transillumination refers to light being transmitted through tissue (i.e. due to excess fluid)



**Differential of a Benign Scrotal Mass**

**HIS BITS**
**H**ydrocele
**I**nfection (epididymitis/orchitis)
**S**perm (spermatocele)
**B**lood (hematocele)
**I**ntestines (hernia)
**T**orsion
**S**ome veins (varicocele)

# Penile Complaints

**Table 24. Penile Complaints**

| Type | Peyronie's Disease | Priapism | Paraphimosis | Phimosis | Premature Ejaculation |
|---|---|---|---|---|---|
| **Definition** | Acquired curvature of penile shaft secondary to fibrous thickening of tunica albuginea | Prolonged erection lasting >4 h in the absence of sexual excitement/desire | Retracted Foreskin (behind glans penis) that cannot be reduced | Inability to retract foreskin over glans penis | Ejaculation prior to when one or both partners desire it, either before or soon after penetration |
| **Etiology** | Etiology unknown<br>Trauma/repeated inflammation<br>Familial predisposition<br>Associated with DM, vascular disease, autoimmunity, Dupuytren's contracture, erectile dysfunction, urethral instrumentation | 50% idiopathic<br>**Ischemic (common)**<br>Thromboembolic (sickle cell)<br>**Non-Ischemic**<br>Trauma<br>Medications<br>Neurogenic | Iatrogenic (post cleaning/ instrumentation)<br>Trauma<br>Infectious (balanitis, balanoposthitis) | Congenital (90% natural separation by age 3)<br>Balanitis<br>Poor Hygiene | Psychological factors<br>Primary: no period of acceptable control<br>Secondary: symptoms after a period of control, not associated with general medical condition |
| **Hx/P/E** | Penile curvature/ shortening<br>Pain with erection<br>Poor erection distal to plaque | Painful erection ± signs of necrosis<br>Note: *non-ischemic (high flow)* priapism may present without pain | Painful, swollen glans penis, foreskin<br>Constricting band proximal to corona<br>Dysuria, decreased urinary stream in children | Limitation and pain when attempting to retract foreskin<br>Balanoposthitis (infection of prepuce) | Ejaculatory latency ≥1 min<br>Inability to control or delay ejaculation<br>Psychological distress |
| **Investigations** | Hx and P/E | Hx and P/E<br>Cavernosal blood gas analysis<br>Doppler US of the penis | Hx and P/E | Hx and P/E | Hx and P/E<br>Testosterone levels if in conjunction with impotence |
| **Treatment** | **Supportive measures:**<br>PDE5 inhibitor for ED<br>NSAID for pain (spontaneous resolution in up to 12%)<br>**Medical management:**<br>Traction device<br>Intralesional verapamil<br>Intralesional collagenase<br>**Surgical management:**<br>Incision/excision of plaque<br>Plication surgery<br>Penile prosthesis | Treat reversible causes<br>**High-flow:**<br>Self-limited<br>Consider arterial embolization<br>**Low-flow:**<br>Needle aspirated decompression<br>Phenylephrine intracorporeal injection q3-5min<br>Surgical shunt no response within 1 h | Manual pressure (with analgesia)<br>Dorsal slit<br>Circumcision (urgent or electively to prevent recurrence) | Proper hygiene<br>Topical corticiosterioids<br>Dorsal slit<br>Circumcision | Rule out medical condition Address psychiatric concerns, counselling<br>**Medication:**<br>SSRI or clomipramine<br>Topical lidocaine-prilocaine |



Testosterone deficiency is an uncommon cause of ED



**Erections POINT AND SHOOT**
**p**arasympathetics = **point**; and
**s**ympathetics/**s**omatics = **shoot**



**Etiology ("IMPOTENCE")**
- **I**atrogenic: pelvic surgery, pelvic radiation
- **M**echanical: Peyronie's, post-priapism
- **P**sychological: depression, stress, anxiety, PTSD, widower syndrome
- **O**cclusive: arterial HTN, DM, smoking, hyperlipidemia, PVD, impaired veno-occlusion
- **T**rauma: penile/pelvic, bicycling
- **E**xtra factors: renal failure, cirrhosis, COPD, sleep apnea, malnutrition
- **N**eurogenic: CNS (e.g. Parkinson's, MS, spinal cord injury, Guillain-Barré, spina bifida, stroke), PNS (e.g. DM, peripheral neuropathy)
- **C**hemical: antihypertensives, sedatives, antidepressants, antipsychotics, anxiolytics, anticholingerics, antihistamines, antiandrogens (including 5-α reductase inhibitors), statins, GnRH agonists, illicit drugs
- **E**ndocrine: DM, hypogonadism, hyperprolactinemia, hypo/hyperthyroid

# Erectile Dysfunction

## Definition
- consistent (>3 mo duration) or recurrent inability to obtain or maintain an adequate erection for satisfactory sexual performance

## Physiology
- erection involves the coordination of psychologic, neurologic, hemodynamic, mechanical, and endocrine components
- nerves: sympathetic (T11-L2), parasympathetic (S2-4), somatic (dorsal penile/pudendal nerves [S2-4])
- erection ("POINT")
  - parasympathetics → NO release → increased cGMP within corpora cavernosa leading to:
    1. arteriolar dilatation
    2. sinusoidal smooth muscle relaxation → increased arterial inflow and compression of penile venous drainage (decreased venous outflow)
- emission ("SHOOT")
  - sensory afferents from glans
  - secretions from prostate, seminal vesicles, and ejaculatory ducts enter prostatic urethra (sympathetics)
- ejaculation ("SHOOT")
  - bladder neck closure (sympathetic)
  - spasmodic contraction of bulbo-cavernosus and pelvic floor musculature (somatic)
- detumescence
  - sympathetic nerves, norepinephrine, endothelin-1 → arteriolar and sinusoidal constriction → penile flaccidity

## Classification

**Table 25. Classification of Erectile Dysfunction**

| | Psychogenic* | Organic* |
|---|---|---|
| **Proportion** | 10% | 90% |
| **Onset** | Sudden | Gradual |
| **Frequency** | Sporadic | All circumstances |
| **Variation** | With partner and circumstance | No |
| **Age** | Younger | Older |
| **Organic Risk Factors (HTN, DM, dyslipidemia)** | No organic risk factors | Risk factors present |
| **Nocturnal/AM Erection** | Present | Absent |

*Combination can co-exist

## Diagnosis
- complete Hx (include sexual, medical, and psychosocial aspects)
- self-administered questionnaires (e.g. International Index of Erectile Function, Sexual Health Inventory for Men Questionnaire, ED Intensity Scale, ED Impact Scale)
- focused P/E, including vascular and neurologic examinations, secondary sexual characteristics
- lab investigations, dependent on clinical picture
  - risk factor evaluation: fasting blood glucose or HbA1c, cholesterol profile
  - optional: TSH, CBC, U/A, testosterone (free and total), prolactin, LH
- specialized testing including nocturnal penile tumescence monitoring usually unnecessary
- evaluation of penile vasculature only relevant with past history of trauma (i.e. pelvic fracture)

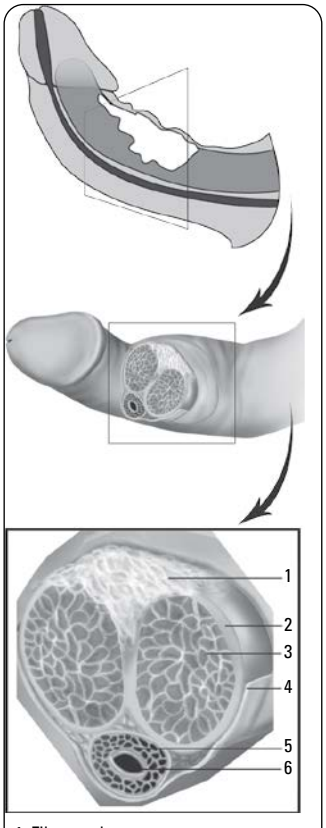
## Treatment
- can often be managed by family doctor, see sidebar for when to refer
- must fully inform patient/partner of options, benefits and complications
- non-invasive
  - lifestyle changes (alcohol, smoking), psychological (sexual counselling and education)
  - change precipitating medications
  - treat underlying causes (DM, CVD, HTN, endocrinopathies)
- minimally invasive
  - oral medication (see *Common Medications*, U44)
    - sildenafil, tadalafil, vardenafil, avanafil (not available in Canada): inhibits PDE-5 to increase intracavernosal cyclic GMP levels
      - all four have similar effectiveness, difference in onset of action is not clinically significant
      - tadalafil has longer half-life, no cyanopsia, and can be taken on empty or full stomach
    - vacuum devices: draw blood into penis via negative pressure, then put ring at base of penis
    - MUSE: male urethral suppository for erection – vasoactive substance (PGE1) capsule inserted into urethra
- invasive
  - intracavernous vasodilator injection/self-injection
    - triple therapy (papaverine, phentolamine, PGE1) or PGE1 alone
    - complications: priapism (overdose), fibrosis of tunica albuginea at site of repeated injections (Peyronie's plaque) and injection site injuries (pain, hematoma, etc.)
- surgical
  - penile implant (last resort): malleable or inflatable
  - penile artery reconstruction (in young men with isolated vascular lesion – investigational)

**When to Consider Referral**

**FAT PEN**
**F**ailed medical therapy
penile **A**natomic abnormality
pelvic/perineal **T**rauma
**P**sychogenic cause
**E**ndocrinopathy
vascular/**N**eurologic assessment

PDE-5 inhibitors are contraindicated in patients on nitrates/nitroglycerin due to severe hypotension

Initial trial of MUSE® or intracavernosal injection should be done under medical supervision




1. Fibrous plaque
2. Tunica albuginea
3. Corpus cavernosum
4. Buck's fascia
5. Corpus spongiosum
6. Urethra

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**Figure 20. Peyronie's disease**

Penile vascular abnormalities may be a marker of risk for CV disease. Young men with vascular ED have 50x higher risk of having a CV event

# Trauma

- see Emergency Medicine, ER7

## Renal Trauma

### Classification According to Severity
- minor
  - contusions and superficial lacerations/hematomas: 90% of all blunt traumas, surgical exploration seldom necessary
- major
  - laceration that extends into medulla and collecting system, major renal vascular injury, shattered kidney

### Etiology
- 80% blunt (MVC, assaults, falls) vs. 20% penetrating (stab wounds and gunshots)

### Clinical Features
- mechanism of injury raises suspicion
- can be hemodynamically unstable secondary to renal vascular injury and/or other sustained injuries: ABCs
- upper abdominal tenderness, flank tenderness, flank contusions, lower rib/vertebral transverse process fracture

### Investigations
- U/A
  - hematuria: requires workup but degree does not correlate with the severity of injury
- imaging
  - CT (contrast, triphasic) if patient stable: look for renal laceration, extravasation of contrast, retroperitoneal hematoma, and associated intra-abdominal organ injury

### Staging (does not necessarily correlate well with clinical status)
- I: contusion/hematoma
- II: <1 cm laceration without urinary extravasation
- III: >1 cm laceration without urinary extravasation
- IV: laceration causing urinary extravasation and/or main arterial or vein injury with contained hematoma
- V: shattered kidney or avulsion of pedicle

### Treatment
- microscopic hematuria + isolated well-staged minor injuries → no hospitalization
- gross hematuria + contusion/minor lacerations → hospitalize, bedrest, repeat CT if bleeding persists
- surgical intervention/minimally invasive angiography and embolization (majority now managed conservatively, non-operatively)
  - absolute indications
    - hemorrhage and hemodynamic instability
  - relative indications
    - non-viable tissue and major laceration
    - urinary extravasation
    - vascular injury
    - expanding or pulsating peri-renal mass
    - laparotomy for associated injury
- follow-up with U/S or CT before discharge, and at 6 wk

### Complications
- HTN in 5% of renal trauma

## Bladder Trauma

### Classification
- contusions: no urinary extravasation, damage to mucosa or muscularis
- intraperitoneal ruptures: often involve the bladder dome
- extraperitoneal ruptures: involve anterior or lateral bladder wall in full bladder

### Etiology
- blunt (MVC, falls, and crush injury) vs. penetrating trauma to lower abdomen, pelvis, or perineum
- blunt trauma is associated with pelvic fracture in 97% of cases

### Clinical Features
- abdominal tenderness, distention, peritonitis, and inability to void
- can be hemodynamically unstable secondary to pelvic fracture, other sustained injuries: ABCs
- suprapubic pain

### Investigations
- U/A: gross hematuria in 90%
- imaging (including CT cystogram and post-drainage films for extravasation)

### Treatment
- penetrating trauma → surgical exploration
- contusion → urethral catheter until hematuria completely resolves
- extraperitoneal bladder perforations → typically non-operative with foley insertion, and follow with cystograms
  - surgery if: infected urine, rectal/vaginal perforation, bony spike into bladder, laparotomy for concurrent injury, bladder neck involvement, persistent urine leak and failed conservative management
- intraperitoneal rupture usually requires surgical repair and suprapubic catheterization

### Complications
- complications of bladder injury itself are rare
- mortality is around 20%, and is usually due to associated injuries rather than bladder rupture

## Urethral Injuries

### Etiology
- posterior urethra
  - common site of injury is junction of membranous and prostatic urethra due to blunt trauma, MVCs, pelvic fracture
  - shearing force on fixed membranous and mobile prostatic urethra
- anterior urethra
  - straddle injury can crush bulbar urethra against pubic rami
- other causes
  - iatrogenic (instrumentation, prosthesis insertion), penile fracture, masturbation with urethral manipulation
- always look for associated bladder rupture

### Clinical Features
- blood at urethral meatus
- high-riding prostate on DRE
- swelling and butterfly perineal hematoma
- penile and/or scrotal hematoma
- sensation of voiding without U/O
- distended bladder



All patients with suspected urethral injury should undergo RUG

### Investigations
- must perform RUG or cystoscopy prior to catheterization

### Treatment
- simple contusions
  - no treatment
- partial urethral disruption
  - very gentle attempt at catheterization by urologist
  - with no resistance to catheterization → Foley x 2-3 wk
  - with resistance to catheterization → suprapubic cystostomy or urethral catheter alignment
- periodic flow rates/urethrograms to evaluate for stricture formation
- complete disruption
  - immediate repair if patient stable, delayed repair if unstable (suprapubic tube in interim)

### Complications
- stricture

# Infertility

### Definition
- failure to conceive after one year of frequent, unprotected and properly timed intercourse
- incidence
  - 15% of all couples (35-40% female, 20% male, 25-30% combined)

## Female Factors

- see Gynecology, GY22

## Male Factors

### Male Reproduction
- hypothalamic-pituitary-testicular axis (HPTA)
  - pulsatile GnRH from hypothalamus acts on anterior pituitary stimulating release of LH and FSH
  - LH acts on Leydig (interstitial) cells → testosterone synthesis and secretion
  - FSH acts on Sertoli cells → structural and metabolic support to developing spermatogenic cells
  - FSH and testosterone support germ cells (responsible for spermatogenesis)
  - sperm route: epididymis → vas deferens → ejaculatory ducts → prostatic urethra

### Etiology
- idiopathic (40-50% infertile males)
- testicular
  - varicocele (35-40% infertile males)
  - tumour
  - congenital (Klinefelter's triad: small, firm testes, gynecomastia, and azoospermia)
  - post-infectious (epididymo-orchitis, STIs, mumps)
  - uncorrected torsion
  - cryptorchidism (<5% of cases)
- obstructive
  - iatrogenic (surgery: see below)
  - infectious (gonorrhea, chlamydia)
  - trauma
  - congenital (absence of vas deferens, CF)
  - bilateral ejaculatory duct obstruction, epididymal obstructions
  - Kartagener's syndrome (autosomal recessive disorder causing defect in action of cilia)
- endocrine (see Endocrinology, E48)
- HPTA (2-3%) e.g. Kallmann's syndrome (congenital hypothalamic hypogonadism), excess prolactin, excess androgens, excess estrogens
- other
  - retrograde ejaculation secondary to surgery
  - medications
  - prior exposure to chemotherapy or pelvic radiation
  - drugs: marijuana, cocaine, tobacco, alcohol
  - increased testicular temperature (sauna, hot baths, tight pants or underwear)
  - chronic disease: e.g. liver, renal

### History
- age of both partners
- medical: past illness, DM, trauma, CF, genetic syndromes, STIs, cryptorchidism
- surgical: vasectomy, herniorrhaphy, orchidopexy, prostate surgery
- fertility: pubertal onset, previous pregnancies, duration of infertility, treatments
- sexual: libido, erection/ejaculation, timing, frequency
- family Hx
- medications: cytotoxic agents, GnRH agonists, anabolic steroids, nitrofurantoin, cimetidine, sulfasalazine, spironolactone, α-blockers
- social Hx: alcohol, tobacco, cocaine, marijuana, school performance/learning disabilities (suggestive of Klinefelter syndrome)
- occupational exposures: radiation, heavy metals

### Physical Exam
- general appearance: sexual development, gynecomastia, obesity, pubic hair
- scrotal exam: size, consistency, and nodularity of testicles; palpation of cord for presence of vas deferens; DRE; valsalva for varicocele

### Investigations
- semen analysis (SA) at least 2 specimens, collected 1-2 wk apart
- hormonal evaluation
  - indicated with abnormal SA (rare to be abnormal with normal SA)
  - testosterone and FSH
  - serum LH and prolactin are measured if testosterone or FSH are abnormal



**Normal Semen Values**
- Volume: 2-5 mL
- Concentration: >15 million sperm/mL
- Morphology: 30% normal forms
- Motility: >40% adequate forward progression
- Liquefaction: complete in 20 min
- pH: 7.2-7.8
- WBC: <10/HPF or $<10^6$ WBC/mL semen

- genetic evaluation
  - chromosomal studies (Klinefelter syndrome – XXY)
  - genetic studies (Y-chromosome microdeletion, CF gene mutation)
- immunologic studies (antisperm antibodies in ejaculate and blood)
- testicular biopsy
- scrotal U/S (varicocele, testicular size)
- vasography (assess patency of vas deferens)

### Treatment

- assessment of partner
- lifestyle
  - regular exercise, healthy diet
  - eliminate alcohol, tobacco and illicit drugs
- medical
  - endocrine therapy (see Endocrinology, E48)
  - treat retrograde ejaculation
  - discontinue anti-sympathomimetic agents, may start α-adrenergic stimulation (phenylpropanolamine, pseudoephedrine, or ephedrine)
  - treat underlying infections
- surgical
  - varicocelectomy (if indicated)
  - vasovasostomy (vasectomy reversal) or epididymovasostomy
  - transurethral resection of blocked ejaculatory ducts
- assisted reproductive technologies (ART)
  - refer to infertility specialist
  - sperm washing + intrauterine insemination (IUI)
  - in vitro fertilization (IVF)
  - intracytoplasmic sperm injection (ICSI) after CF screening of patient and partner in patients with congenital bilateral absence of vas deferens

**Common Terminology on SA**
- Teratospermia: Abnormal morphology
- Asthenospermia: Abnormal motility
- Oligospermia: Decreased sperm count
- Azoospermia: Absent sperm in semen
- Mixed types: i.e. oligoasthenospermia

Mutation of cystic fibrosis transmembrane conductance regulator (CFTR) gene is associated with congenital bilateral absence of vas deferens and epididymal cysts, even if patient manifests no symptoms of CF

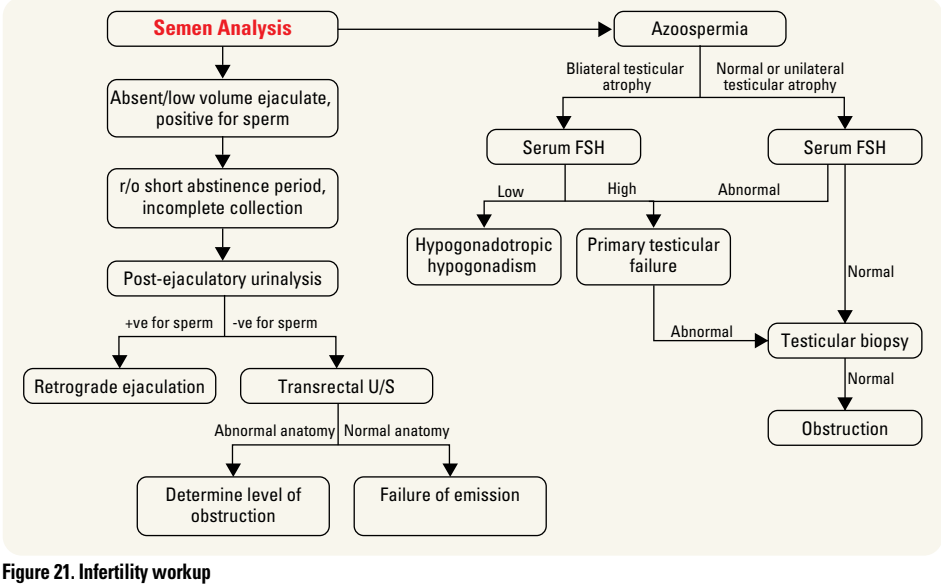



**Figure 21. Infertility workup**

**WHO Guidelines**
**Male Infertility Factors**

**SPERM COUNT**
**S**ystemic factor/Smoking
**P**sychological illness
**E**ndocrinopathy
**R**etrograde ejaculation
**M**edications
**C**hronic disease
**O**bstructive
**U**nexplained
**N**arcotics
**T**esticular

# Pediatric Urology

## Congenital Abnormalities

- not uncommon; 1/200 have congenital abnormalities of the GU tract
- six common presentations of congenital urological abnormalities

### 1. ANTENATAL HYDRONEPHROSIS

#### Epidemiology

- 1-5% fetal U/S, some detectable as early as first trimester
- most common urological consultation in perinatal period and one of most common U/S abnormalities of pregnancy

Majority of antenatal hydronephroses resolve during pregnancy or within the first year of life

#### Differential Diagnosis

- transient primary hydronephrosis
- UPJ obstruction
- VUR

- UVJ obstruction or primary non-obstructive megaureter
- ureterocele
- ectopic ureter
- causes of megacystitis (i.e. PUV, Prune Belly syndrome)

### Treatment
- antenatal in utero intervention rarely indicated unless evidence of lower urinary tract obstruction with oligohydramnios
- ABx prophylaxis at birth to reduce UTI rates is controversial but may be beneficial to infants with high grade hydronephrosis, dilated ureter, or bladder abnormality. Commonly used ABx include: amoxicillin, cephalexin, and trimethoprim.

## 2. POSTERIOR URETHRAL VALVES

### Epidemiology
- the most common congenital obstructive urethral lesion in male infants

### Pathophysiology
- abnormal mucosal folds at the distal prostatic urethra causing varying degrees of obstruction

### Clinical Feature
- dependent on age
  - antenatal: bilateral hydronephrosis, distended bladder, oligohydramnios
  - neonatal (recognized at birth): palpable abdominal mass (distended bladder, hydronephrosis), urinary ascites (transudation of retroperitoneal urine), respiratory distress (pulmonary hypoplasia from oligohydramnios), weak urinary stream
  - neonatal (not recognized at birth): within weeks present with urosepsis, dehydration, electrolyte abnormalities, failure to thrive; rule out pyloric stenosis, which may present similarly
  - toddlers: UTIs or voiding dysfunction
  - school-aged boys: voiding dysfunction → urinary incontinence
- associated findings include renal dysplasia and secondary VUR

### Investigations
- most commonly recognized on prenatal U/S → bilateral hydronephrosis, thickened bladder, dilated posterior urethra ("keyhole sign"), oligohydramnios in a male fetus
- VCUG → dilated and elongated posterior urethra, trabeculated bladder, VUR

### Treatment
- immediate catheterization to relieve obstruction, followed by cystoscopic resection of PUV when baby is stable
- if resection of PUV is not possible, vesicostomy is indicated

## 3. URETEROPELVIC JUNCTION OBSTRUCTION

### Etiology
- unclear: adynamic ureteral segment, stenosis, strictures, extrinsic compression, aberrant blood vessels
- can rarely be secondary to tumour, stone, etc. in children

### Epidemiology
- the most common congenital defect of the ureter
- M:F = 2:1
- up to 40% bilateral, which may be associated with worse prognosis

### Clinical Feature
- symptoms depend on severity and age at diagnosis (mostly asymptomatic finding on antenatal U/S)
  - infants: abdominal mass, urinary infection
  - children: pain, vomiting, failure to thrive
- some cases are diagnosed after puberty and into adulthood
  - in adolescents and adults, the symptoms may be triggered by episodes of increased diuresis, such as following alcohol ingestion (Dietl's crisis)

### Investigations
- antenatal: serial U/S most common, and renal scan ± furosemide

### Treatment
- surgical correction (pyeloplasty), consider nephrectomy if <15% differential renal function

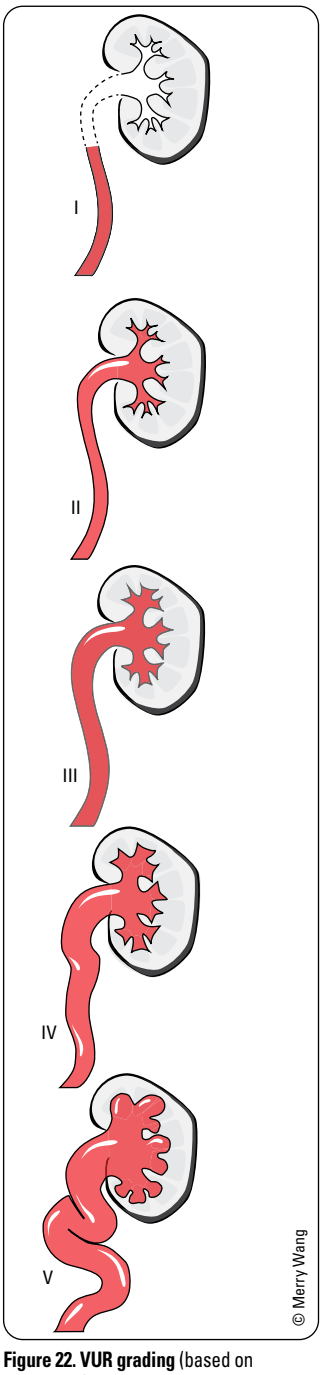



**Figure 22. VUR grading** (based on cystogram)

**VUR Grading (based on cystogram)**
- Grade I: ureters only fill
- Grade II: ureters and pelvis fill
- Grade III: ureters and pelvis fill with some dilatation
- Grade IV: ureters, pelvis, and calyces fill with significant dilatation
- Grade V: ureters, pelvis, and calyces fill with major dilatation and tortuosity

Defer circumcision in patients with hypospadias

## 4. VESICOURETERAL REFLUX

### Definition
- retrograde passage of urine from the bladder, through the UVJ, into the ureter

### Classification
- primary reflux: incompetent or inadequate closure of UVJ
  - lateral ureteral insertion, short submucosal segment
- secondary reflux: abnormally high intravesical pressure resulting in failure of UVJ closure
  - often associated with anatomic (PUV) or functional (neuropathic) bladder dysfunction

### Epidemiology
- estimated ~1% of newborns, but not well known
- incidence and clinical relevance higher in children with febrile UTIs and prenatal hydronephrosis
- risk factors: race (white > black), female gender, age (<2 yr), genetic predisposition

### Investigations
- focused Hx, particularly of voiding dysfunction (frequency, urgency, diurnal enuresis, constipation, encopresis)
  - also screen for infections (UTI, pyelonephritis, urosepsis) and renal failure (uremia, HTN)
- initial evaluation of renal status, growth parameters, and blood pressure is warranted in any child with VUR due to relatively high incidence of renal scarring
  - height, weight, blood pressure
  - serum Cr
  - U/A, C&S
  - renal U/S
  - DMSA renal scan if at high risk (greater sensitivity in detecting structural defects associated with dysplasia, renal scarring or pyelonephritis; entails radiation exposure)
  - sibling family screening is controversial

### Treatment
- spontaneous resolution in 60% of primary reflux
  - in lower grades (I-III), goal is to prevent infection or renal damage via medical treatment
- medical treatment: daily ABx prophylaxis at half the treatment dose for acute infection (see Table 8 - TMP/SMX, trimethoprim, amoxicillin, or nitrofurantoin)
- surgical treatment: ureteral reimplantation ± ureteroplasty, or subureteral injection with bulking agents (Deflux® or Macroplastique®)
  - indications include failure of medical management, renal scarring (e.g. renal insufficiency, HTN), breakthrough UTIs, persistent high grade (IV or V) reflux

## 5. HYPOSPADIAS

### Definition
- a condition in which the urethral meatus opens on the ventral side of the penis, proximal to the normal location in the glans penis
- depending on severity, may result in difficulty directing urinary stream, having intercourse or depositing sperm in vagina

### Epidemiology
- very common; 1/300 live male births
- distal hypospadias more common than proximal
- white >> black
- may be associated with ventral penile curvature, disorders of sexual differentiation, undescended testicles or inguinal hernia

### Treatment
- early surgical correction; optimal repair before 2 yr
- neonatal circumcision should be deferred because the foreskin may be utilized in the correction

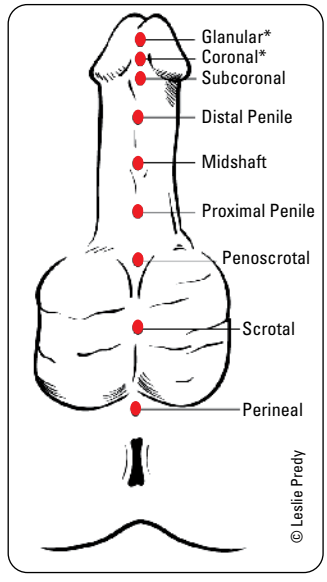



**Figure 23. Classification of hypospadias**
(*account for 75%)

## 6. EXSTROPHY-EPISPADIAS COMPLEX

### Definition
- a spectrum of defects depending on the timing of the rupture of the cloacal membrane
  - bladder exstrophy: congenital defect of a portion of lower abdominal and anterior bladder wall, with exposure of the bladder lumen
  - cloacal exstrophy
    - exposed bladder and bowel with imperforate anus
    - associated with spina bifida in >50%
  - epispadias (least severe)
    - urethra opens on dorsal aspect of the penis, often associated with penile curvature

### Etiology
- represents failure of closure of the cloacal membrane, resulting in the bladder and urethra opening directly through the abdominal wall

### Epidemiology
- rare: incidence 1/30,000, M:F = 3:1 predominance
- high morbidity → multiple reconstructive surgeries, incontinence, infertility, reflux

### Treatment
- surgical correction at birth
- later corrections for incontinence, VUR, and low bladder capacity may be needed

## Nephroblastoma (Wilms' Tumour)

### Etiology
- arises from abnormal proliferation of metanephric blastema

### Epidemiology
- 5-10: 5% of all childhood cancers, 5% bilateral, 10% associated with congenital malformation syndromes
- most common primary malignant renal tumour of childhood
- average age of incidence is 3 yr

**Associated Syndromes of Wilms' Tumour**
Wilms' aniridia genital anomaly retardation
Beckwith-Wiedemann syndrome
Denys-Drash syndrome

### Clinical Features
- abdominal mass: large, firm, unilateral (80%)
- HTN (25%)
- flank tenderness (30-40%)
- microscopic hematuria (12-25%)
- nausea/vomiting

### Treatment
- always investigate contralateral kidney and renal vein (for tumour thrombus)
- unilateral disease: radical nephrectomy ± radiation ± chemotherapy
- bilateral disease: nephron-sparing surgery following neoadjuvant chemotherapy

### Prognosis
- 5 yr survival 80%

## Cryptorchidism/Ectopic Testes

**Normal Testicular Development and Descent in Utero**
**2nd mo**: Testicle begins to form
**4th mo**: Begins to take on its normal appearance and migrates from its origin at the kidney to the internal inguinal ring
**7th mo**: The testis, surrounded in peritoneal covering, begins to descend through the internal ring, inguinal canal and external ring to terminate in the scrotum

### Definition
- abnormal location of testes somewhere along the normal path of descent (external inguinal ring > inguinal canal > abdominal)
- Denis Browne pouch (between external oblique fascia and Scarpa's fascia) most common
- differential diagnosis:
  - retractile testes
  - atrophic testes
  - disorders of sexual differentiation (bilateral impalpable gonads)

### Epidemiology
- 1.0-4.6% of full term newborns, increased risk in pre-terms
- 0.7-1.0% at 1 yr

### Treatment
- orchiopexy
- hormonal therapy not proven to be of benefit over standard surgical treatment

### Prognosis
- reduction in fertility
  - untreated bilateral cryptorchidism: ~100% infertility, due to Leydig and germ cell loss
  - paternity rates: 33-65%, 90%, and 93% in formerly bilateral cryptorchid, formerly unilateral cryptorchid, and normal men, respectively
- increased malignancy risk
  - intra-abdominal > inguinal
  - surgical correction facilitates testicular monitoring and may reduce malignancy risk
- increased risk of testicular torsion (reduced by surgical correction)

# Disorders of Sexual Differentiation

### Definition
- formerly known as intersex disorders: considered social emergency
- abnormal genitalia for chromosomal sex due to the undermasculinization of males or the virilization of females

### Classification
1. 46 XY DSD
   - defect in testicular synthesis of androgens
   - androgen resistance in target tissues
   - palpable gonad
2. 46 XX DSD
   - most due to CAH (21-hydroxylase deficiency most common enzymatic defect) → shunt in steroid biosynthetic pathway leading to excess androgens
   - undiagnosed and untreated CAH can be associated with life-threatening electrolyte abnormalities in the newborn (salt-wasting CAH)
3. ovotesticular DSD
4. mixed gonadal dysgenesis (46 XY/45 XO most common karyotype)
   - presence of Y chromosome → partial testis determination to varying degrees



A phenotypic male newborn with bilateral non-palpable testicles should be considered 46XX with salt-wasting CAH and must undergo proper evaluation prior to discharge

### Diagnosis
- thorough family Hx noting any consanguinity
- maternal Hx, especially medication/drug use during pregnancy (maternal hyperandrogenemia)
- P/E: palpable gonad (= chromosomal male), hyperpigmentation, evidence of dehydration, HTN, stretched phallus length, position of urethral meatus
- laboratory tests
  - plasma 17-OH-progesterone (after 36 h of life) → increased in CAH
  - plasma 11-deoxycortisol → increased in 11-β-hydroxylase deficiency
  - basal adrenal steroid levels
  - serum testosterone and DHT pre- and post-hCG stimulation (2000 IU/d for 4 d)
  - serum electrolytes
  - chromosomal evaluation including sex karyotype
- U/S of adrenals, gonads, uterus, and fallopian tubes
- endoscopy and genitography of urogenital sinus

### Treatment
- steroid supplementation as indicated (e.g. CAH)
- sex assignment after extensive family consultation
  - must consider capacity for sexually functioning genitalia in adulthood, fertility potential, and psychological impact
- reconstruction of external genitalia between 6 and 12 mo
- long-term psychological guidance and support for both patient and family

# Enuresis

- see Pediatrics, P9

# Selected Urological Procedures

### Bladder Catheterization
- catheter size measured by the French (Fr) scale – circumference in mm
- each 1 mm increase in diameter = approximately 3 Fr increase (standard size 14-18 Fr)
- should be removed as soon as possible to reduce the risk of UTI

### Continuous Catheterization
- indications
  - accurate monitoring of U/O
  - relief of urinary retention due to medication, neurogenic bladder, or intravesical obstruction
  - temporary therapy for urinary incontinence
  - perineal wounds
  - clot prevention (22-24 Fr) for CBI
  - intra- and post-operative
  - comfort for end of life care

### Alternatives to Continuous Catheterization
- intermittent catheterization
  - PVR measurement
  - to obtain sterile diagnostic specimens for U/A, urine C&S
  - management of neurogenic bladder or chronic urinary retention
- condom catheter
- suprapubic catheter

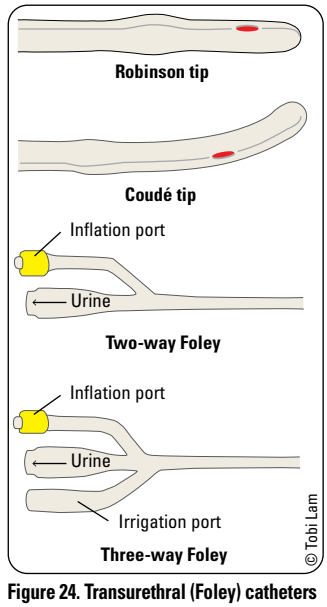



Figure 24. Transurethral (Foley) catheters

### Causes of Difficult Catheterizations and Treatment
- patient discomfort → use sufficient lubrication (± xylocaine)
- collapsing catheter → lubrication as above ± firmer or larger catheter (silastic catheter)
- meatal/urethral stricture → dilate with progressively larger catheters/balloon catheter
- traumatic injury: repeated prior attempts at catheterization have created traumatic false passage
- BPH → use Coudé catheter as angled tip can help navigate around enlarged prostate
- urethral disruption/obstruction → filiform and followers or suprapubic catheterization
- anxious patient → anxiolytic medication

### Complications of Catheterization
- infection: UTI, bladder fistula, bladder perforation (rare)
- meatal/urethral trauma

### Contraindications
- trauma: blood at the urinary meatus, scrotal hematoma, pelvic fracture, and/or high riding prostate

## Circumcision

### Definition
- removal of some or all of the foreskin from the penis

### Epidemiology
- 30% worldwide
- frequency varies with geography, religious affiliation, socioeconomic status

### Medical Indications
- pathological phimosis and recurrent paraphimosis
- recurrent UTIs (particularly in infants and in association with other urinary abnormalities)
- balanitis xerotica obliterans or other chronic inflammatory conditions

### Contraindications
- unstable or sick infant
- congenital genital abnormalities (hypospadias, epispadias, penoscrotal webbing, concealed penis, ventral curvature)
- family Hx of bleeding disorders warrants investigation prior to circumcision

### Complications
- early: bleeding, infection, glans injury, amputation, slippage of circumcision device, rarely death
- late: redundant foreskin, cosmetic issues, inclusion cysts, adhesions/skin bridges, suture sinus tracts, ventral curvature, secondary buried penis, phimosis, fistula, meatal stenosis
- 0.6-2% complication rate

**Newborn Male Circumcision**
Paediatr Child Health 2015;20:311-15
**Study:** Position Statement by the Canadian Paediatric Society (CPS) reaffirmed Feb 28, 2018
**Recommendations:** With the exception of some high-risk populations and circumstances where circumcision is indicated for disease prevention, reduction and/or treatment, the routine circumcision of every newborn male is not recommended.

**Male Circumcision for Prevention of Heterosexual Acquisition of HIV in Men**
Cochrane DB Syst Rev 2009;2:CD003362
**Purpose**: To evaluate the effectiveness and safety of male circumcision for preventing acquisition of HIV in heterosexual men.
**Methods**: The analyzed data is from three randomized controlled trials to assess the efficacy of male circumcision for preventing HIV acquisition in men in Africa.
**Results**: Medical male circumcision reduces the acquisition of HIV by heterosexual men (38-66% over 24 mo).

## Cystoscopy

### Objective
- endoscopic inspection of the lower urinary tract (urethra, prostate, bladder, and ureteral orifices), samples for cytology
- scopes can be flexible or rigid
- done under local anesthesia only, for majority

### Indications
- hematuria
- LUTS (storage or voiding)
- urethral and bladder neck strictures
- bladder stones
- bladder tumour surveillance
- evaluation of upper tracts with retrograde pyelography (ureteric stents, catheters)

### Complications
- during procedure
  - bleeding
  - anesthetic-related
  - perforation (rare)
- post-procedure (short-term)
  - infections (antibiotic prophylaxis recommended)
  - urinary retention
- post-procedure (long-term)
  - stricture

# Radical Prostatectomy

## Objective
- the removal of the entire prostate and prostatic capsule via a lower midline abdominal incision, laparoscopically or robotically
  - internal iliac and obturator vessel lymph nodes may also be dissected and sent for pathology (dependent on risk: clinical stage, grade, PSA)
  - seminal vesicle vessels are also partially or completely removed

## Indications
- treatment for localized prostate cancer

## Complications
- immediate (intraoperative)
  - blood loss
  - rectal injury (extremely rare)
  - ureteral injury (extremely rare)
- perioperative
  - lymphocele formation if concurrent pelvic lymphadenectomy performed)
  - blood loss
  - urine leak from anastomosis
- late
  - moderate to severe stress urinary incontinence (3-10%)
  - mild stress urinary incontinence (20%)
  - ED (~50%, depending on whether one, both, or neither of the neurovascular bundles are involved in extracapsular extension of tumour)

**Retropubic, Laparoscopic, and Robot-Assisted Radical Prostatectomy: A Critical Review of Outcomes Reported by High-Volume Centres**
J Endourology 2010;24:2003-2015
**Study**: A systematic review to compare perioperative outcomes, positive surgical margin (PSM) rates, and functional outcomes in retropubic radical prostatectomy (RRP) laparoscopic RP (LRP) and robot-assisted radical prostatectomy (RARP).
**Methods**: Medline database was searched. Weighted means (based on number of participants in each study) were calculated for all outcomes.
**Results**: 58 articles were reviewed. LRP and RARP were associated with better perioperative outcomes compared to RRP. RRP, LRP, and RARP had similar post-operative complication rates ranging from 10.3-10.98%. RARP had a lower overall PSM rate than LRP, and RRP. RARP had the highest continence rate and mean potency rates.
**Conclusion**: In high-volume centres, RRP, LRP and RARP are safe options for treating patients with localized prostate cancer. LRP and RARP are associated with better perioperative outcomes and RARP showed lower PSM rates, higher potency and continence compared to RRP and LRP.

# Transurethral Resection of the Prostate

## Objective
- to partially resect the periurethral portion of the prostate (transition zone) to decrease symptoms of urinary tract obstruction
- accomplished via a transurethral (cystoscopic) approach using an electrocautery loop, irrigation (glycine), and illumination
- not a cancer operation

## Indications
- obstructive uropathy (large bladder diverticula, renal insufficiency)
- refractory urinary retention
- recurrent UTIs
- recurrent gross hematuria
- bladder stones
- intolerance/failure of medical therapy

## Complications
- acute
  - intra- or extraperitoneal rupture of the bladder
  - rectal perforation
  - incontinence
  - incision of the ureteral orifice (with subsequent reflux or ureteral stricture)
  - hemorrhage
  - epididymitis
  - sepsis
  - transurethral resection syndrome (also called "post-TURP syndrome")
    - caused by absorption of a large volume of the hypotonic irrigation solution used, usually through perforated venous sinusoids, leading to a hypervolemic hyponatremic state
    - characterized by dilutional hyponatremia, confusion, nausea, vomiting, HTN, bradycardia, visual disturbances, CHF, and pulmonary edema
    - treat with diuresis and (if severe) hypertonic saline administration
- chronic
  - retrograde ejaculation (>75%)
  - ED (5-10% risk increases with increasing use of cautery)
  - incontinence (<1%)
  - urethral stricture
  - bladder neck contracture

# Extracorporeal Shock Wave Lithotripsy

### Objective
- to treat renal and ureteral calculi (proximal, middle or distal) which cannot pass through the urinary tract naturally
- shockwaves focused onto stone → fragmentation, allowing stone fragments to pass spontaneously and less painfully

### Indications
- potential first-line therapy for renal and ureteral calculi <2 cm
- individuals with calculi in solitary kidney
- individuals with HTN, DM or renal insufficiency
- patient preference and wait-times play a large role in stone management

### Contraindications
- acute UTI or urosepsis
- bleeding disorder or coagulopathy
- pregnancy
- uncontrolled HTN
- obstruction distal to stone (ESWL can be used after stent or nephrostomy inserted)

### Complications
- bacteriuria
- bacteremia
- post-procedure hematuria
- ureteric obstruction (by stone fragments)
- peri-nephric hematoma

# Common Medications

**Table 26. Erectile Dysfunction Medications**

| Drug | Class | Mechanism | Adverse Effects |
|---|---|---|---|
| sildenafil<br>tadalafil<br>vardenafil (PDE5s for use when some erection present) | Phosphodiesterase 5 inhibitor | Selective inhibition of PDE5 (enzyme which degrades cGMP)<br>Leads to sinusoidal smooth muscle relaxation, increased blood flow and erection | Severe hypotension (very rare)<br>Flushing, headaches, dyspepsia<br>Contraindicated if Hx of priapism, or in conditions predisposing to priapism (leukemia, myelofibrosis, polycythemia, sickle cell disease)<br>Contraindicated with nitrates |
| alprostadil (MUSE®), $PGE_1$ + phentolamine + papaverine mixture | Prostaglandin $E_1$ | Activation of cAMP, relaxing sinusoidal smooth muscle<br>Local release (urethral suppository) | Penile pain<br>Presyncope |
| alprostadil, papaverine (intracavernosal injection)<br><br>triple therapy also used: papaverine, phentolamine, $PGE_1$ | See above | See above | Thickening of tunica albuginea at site of repeated injections (Peyronie's plaque)<br>Painful erection<br>Hematoma<br>Contraindicated if Hx of priapism, or in high risk of priapism |

**Table 27. Benign Prostatic Hyperplasia Medications**

| Drug | Class | Mechanism | Adverse Effects |
|---|---|---|---|
| terazosin<br>doxazosin | $\alpha_1$ blockers | α-adrenergic antagonists reduce stromal smooth muscle tone<br>Reduce dynamic component of bladder outlet obstruction | Presyncope<br>Leg edema<br>Retrograde ejaculation<br>Headache<br>Asthenia<br>Nasal congestion |
| tamsulosin<br>alfuzosin<br>silodosin | $\alpha_{1A}$ selective | | |
| finasteride<br>dutasteride | 5-α reductase inhibitor | Blocks conversion of testosterone to DHT<br>Reduces static component of bladder outlet obstruction<br>Reduces prostatic volume | Sexual dysfunction<br>PSA decreases |

**Table 28. Prostatic Carcinoma Medications (N>0, M>0)**

| Drug | Class | Mechanism | Adverse Effects |
|---|---|---|---|
| leuprolide, goserelin *"androgen deprivation therapy"* | GnRH agonist | Initially stimulates LH, increasing testosterone and causing "flare" (initially increases bone pain)<br>Later causes low testosterone | Hot flashes<br>Headache<br>Decreased libido |
| degarelix | GnRH antagonist | Competitively binds to the pituitary gland GnRH receptors, thereby reducing the release of LH, FSH and consequently testosterone by testes | Back pain<br>Breast enlargement<br>Decreased libido<br>Hot flashes<br>Headache<br>Slow or fast heartbeat |
| *cyproterone acetate | Steroidal antiandrogen | Competes with DHT for intracellular receptors:<br>1. Prevent flare produced by GnRH agonist<br>2. Use for complete androgen blockade<br>3. May preserve potency | |
| flutamide, bicalutamide | Non-steroidal antiandrogen | As above | Hepatotoxic: AST/ALT monitoring |
| abiraterone | Non-steroidal antiandrogen | Irreversible CYP17 inhibition, blocking synthesis of androgens in tumour, testis, and adrenal glands | Adrenal insufficiency (concurrent treatment with steroids often required)<br>Hypertriglyceridemia<br>Peripheral edema |
| enzalutamide | Non-steroidal antiandrogen | Androgen receptor signaling inhibitor (full antagonist) | Peripheral edema<br>Fatigue and weakness<br>Hot flashes |

*Very rarely used

**Table 29. Continence Agents and Overactive Bladder Medications**

| Drug | Class | Mechanism | Indication | Adverse Effects |
|---|---|---|---|---|
| oxybutynin | Antispasmotic | Inhibits action of ACh on smooth muscle<br>Decreases frequency of uninhibited detrusor contraction<br>Diminishes initial urge to void | Overactive bladder<br>Urge incontinence + urgency + frequency | Dry mouth<br>Blurred vision<br>Constipation<br>Supraventricular tachycardia |
| oxybutynin<br>tolterodine<br>trospium<br>solifenacin<br>darifenacin<br>fesoterodine<br>propiverine | Anticholinergic | Muscarinic receptor antagonist<br>Selective for bladder<br>Increases bladder volume<br>Decreases detrusor pressure | Overactive bladder<br>Urge incontinence + urgency + frequency | As above |
| mirabegron | β3 agonist | Beta sympathetic receptor blocker in the bladder; relaxes bladder during storage phase | Overactive bladder<br>Urge incontinence + urgency + frequency | Blood pressure should be monitored |
| imipramine | Tricyclic antidepressant | Sympathomimetic effects: urinary sphincter contraction<br>Anticholinergic effects: detrusor relaxation | Stress and urge incontinence | As above<br>Weight gain<br>Orthostatic hypotension<br>Prolonged PR interval |
| Botulinum toxin A bladder injections | Neurotoxin | Prevents the release of neurotransmitters | Refractory OAB incontinence both neurogenic and non-neurogenic | Urinary retention, UTI |

Note: All anticholinergics are equally effective and long-acting formulations are better tolerated. Newer muscarinic M3 receptor specific agents (solifenacin, darifenacin) are equally efficacious as older drugs, however, RCTs based on head-to-head comparison to long acting formulations are lacking.

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# VS Vascular Surgery

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# Acronyms

| | |
|---|---|
| AAA | abdominal aortic aneurysm |
| ABI | ankle-brachial index |
| ACEI | angiotensin converting enzyme inhibitor |
| AFib | atrial fibrillation |
| AKA | above-knee amputation |
| AKI | acute kidney injury |
| ALI | acute limb ischemia |
| aPTT | activated partial thromboplastin time (i.e. PTT) |
| ASA | acetylsalicylic acid (Aspirin®) |
| AT | anterior tibial artery |
| BKA | below-knee amputation |
| BMT | best medical therapy |
| BP | blood pressure |
| CABG | coronary artery bypass graft |
| CAD | coronary artery disease |
| CAS | carotid artery angioplasty + stenting |
| CBC | complete blood count |
| CCB | calcium channel blocker |
| CLI | critical limb ischemia |
| CTA | computed tomography angiography |
| CVA | cerebrovascular accident |
| CVD | cerebrovascular disease |
| CVI | chronic venous insufficiency |
| CXR | chest x-ray |
| DIC | disseminated intravascular coagulation |
| DM | diabetes mellitus |
| DVT | deep vein thrombosis |
| ECASA | enteric coated ASA |
| ECG | electrocardiogram |
| Echo | echocardiogram |
| ET | essential thrombocythemia |
| EVAR | endovascular aortic aneurysm repair |
| EVLT | endovenous laser therapy |
| GSV | greater saphenous vein |
| HITS | heparin-induced thrombocytopenia syndrome |
| HITT | heparin-induced thrombocytopenia with thrombosis |
| HTN | hypertension |
| IBD | inflammatory bowel disease |
| INR | international normalized ratio |
| LFT | liver function test |
| LMWH | low molecular weight heparin |
| LSV | lesser saphenous vein |
| MCA | middle cerebral artery |
| MRA | magnetic resonance angiography |
| MSK | musculoskeletal |
| OCP | oral contraceptive pill |
| PAD | Peripheral Arterial Disease |
| PE | pulmonary embolism |
| PT | prothrombin time |
| PTT | partial thromboplastin time (i.e. aPTT) |
| PVD | peripheral vascular disease |
| RIND | reversible ischemic neurologic deficit |
| sBP | systolic blood pressure |
| SFA | superficial femoral artery |
| SVT | superficial venous thrombosis |
| TAA | thoracic aortic aneurysm |
| TEE | transesophageal echocardiography |
| TEVAR | thoracic endovascular aortic aneurysm repair |
| TIA | transient ischemic attack |
| TTE | transthoracic echocardiogram |

# Peripheral Arterial Disease (PAD)

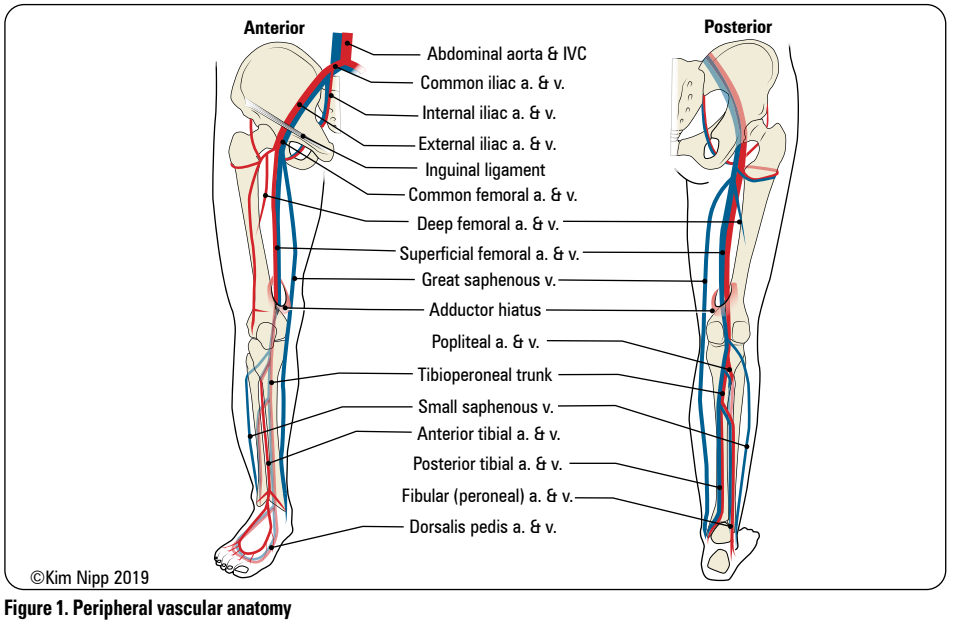



**Figure 1. Peripheral vascular anatomy**

## Acute Arterial Ischemia

### Definition

- acute occlusion of a peripheral artery that often threatens limb viability
  - urgent management required as skeletal muscle can tolerate 6 h of total ischemia before irreversible damage; exception is acute-on-chronic occlusion, where previously developed collaterals provide minimal perfusion
- tends to be lower extremity > upper extremity; femoropopliteal > aortoiliac
- paralysis with complete loss of sensation is sign of late ischemia

### Etiology and Risk Factors

- embolism
  - cardiac: arrhythmias, endocarditis, MI, LV aneurysm, myxoma/cardiac tumour, paradoxical embolism, valvular heart disease
  - non-cardiac: mural thrombus within arterial aneurysms, atheroembolism
- thrombosis
  - atherosclerotic obstruction
  - vasospasm
  - aortic or arterial dissection
  - arterial transection

- embolism vs. thrombosis
  - thrombosis is more common than embolism; usually in superficial femoral artery
  - existing atherosclerotic plaques can rupture causing thrombosis
  - previous vascular grafts/reconstructions can fail and thrombose leading to acute presentation
  - hypercoagulable states can contribute to thrombosis
  - embolism generally results in greater degree of ischemia due to lack of collaterals
  - suspect embolism in patients with the following features:
    - acute onset (patient able to accurately recall the moment of the event)
    - history of embolism
    - known embolic source (e.g. cardiac arrhythmias)
    - no prior history of intermittent claudication
    - normal pulse and Doppler in unaffected limb
- Dx: iatrogenic (e.g. occlusion at arterial access site), compressive, traumatic (blunt or penetrating injuries) causes of acute limb ischemia

## Clinical Features

- **6 Ps** – all may not be present
  - **P**ain
    - may be constant or elicited by passive movement
    - absent in 20% of cases
  - **P**allor: pale
    - within a few hours becomes mottled cyanosis
  - **P**aresthesia
    - light touch lost first then other sensory modalities
  - **P**aralysis/**P**ower loss:
    - most important, heralds impending non-salvageable limb
  - **P**olar/**P**oikilothermia: cold
    - leg becomes cold
  - **P**ulselessness
    - helpful to determine site of occlusion
    - not always reliable

**Acute Aortoiliac Occlusion**
If a patient presents with new onset bilateral critical limb ischemia, suspect possible occlusion of the aorta or aortoiliac segment. Etiologies include thrombosis or rupture of AAA, aortic dissection, or large saddle embolism

## Investigations

- history and physical exam are essential: depending on degree of ischemia one may have to forego investigations and go straight to the operating room
- determine Rutherford classification (Table 1) based on physical findings and Doppler signals
- Ankle Brachial Index (ABI): extension of physical exam, easily performed at bedside
- ECG, troponin: rule out recent MI or arrhythmia
- CBC: rule out leukocytosis, thrombocytosis or thrombocytopenia in patients receiving heparin (may suggest HITS)
- PT/INR, PTT: patient anticoagulated/sub-therapeutic INR
- Echo: identify wall motion abnormalities, intracardiac thrombus, valvular disease, aortic dissection (Type A)
- CT angiogram: identify underlying atherosclerosis, aneurysm, aortic dissection, identify embolic source, identify other end organs with emboli (e.g. splenic/renal infarcts), identify level of the occlusion and extent
- Angiography: can be obtained in OR as part of intervention or for treatment planning

**Hypercoagulable States**

**Congenital**
- Group I (reduced anticoagulants)
  - Antithrombin
  - Protein C
  - Protein S
- Group II (increased coagulants)
  - Factor V Leiden
  - Prothrombin
  - Factor VIII
  - Hyper-homocysteinemia

**Acquired**
- Immobility
- Cancer
- Pregnancy/Systemic hormonal contraceptives/HRT
- Antiphospholipid antibody syndrome
- Inflammatory disorders (e.g. IBD)
- Myeloproliferative disorders (e.g. ET)
- Nephrotic syndrome (acquired deficit in Protein C and S)
- DIC
- HITT

**Table 1. Rutherford ALI Classification**

| Category | Description/Prognosis | Findings | | Doppler Signals | |
|---|---|---|---|---|---|
| | | Sensory Loss | Muscle Weakness | Arterial | Venous |
| **I Viable** | Not immediately threatened | None | None | Audible | Audible |
| **II Threatened** | | | | | |
| **IIa Marginally** | Salvageable if promptly treated | Minimal (toes) or none | None | Inaudible | Audible |
| **IIb Immediately** | Salvageable with immediate revascularization | More than toes, associated with rest pain | Mild, moderate | Inaudible | Audible |
| **III Irreversible** | Major tissue loss or permanent nerve damage inevitable | Profound, anesthetic | Profound, paralysis (rigor) | Inaudible | Inaudible |

Adapted from: Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg. 1997;26:517-38.

### Treatment
- immediate heparinization with weight-based bolus (80 Units/kg) and continuous infusion to titrate PTT to 70-90s
- if impaired neurovascular status: emergent revascularization (Rutherford category IIb)
- if intact neurovascular status: may have time for workup (including CT angiogram)
- identify and treat underlying cause
  - embolus: embolectomy
  - thrombus: thrombectomy ± bypass graft ± endovascular therapy
  - irreversible ischemia (i.e. Rutherford category III): primary amputation or palliation/comfort measures
- continue heparin post-operatively, start oral anticoagulant post-operatively when stable x 3 mo or longer depending on underlying etiology and other comorbidities

### Complications
- local: compartment syndrome (see Orthopedic Surgery, OR10) with prolonged ischemia; requires 4-compartment (anterior/lateral/superficial and deep posterior) fasciotomy
- heart: risk of arrhythmia, MI, cardiac arrest and death with reperfusion injury
- kidneys/other organs: renal failure and multi-organ failure due to toxic metabolites from ischemic muscle, rhabdomyolysis
- up to 10% chance of metachronous embolism

### Prognosis
- 12-15% mortality rate
- 5-40% morbidity rate (amputation)

## Chronic Limb Ischemia/Peripheral Arterial Disease (PAD)

### Definition
- chronic ischemia due to inadequate arterial supply to meet cellular metabolic demands during walking (claudication) or at rest (critical limb ischemia)

### Etiology and Risk Factors
- predominantly due to atherosclerosis (for pathogenesis, see Cardiology and Cardiac Surgery, C25); primarily occurs in the lower extremities
- conventional risk factors: smoking, DM, hyperlipidemia, and hypertension
- predisposing risk factors: advanced age, obesity, sedentary lifestyle, and PMHx or FMHx PAD/CAD/CVD

### Clinical Features
- claudication:
  1. pain with exertion: usually in calves or any exercising muscle group (within the muscle belly)
  2. relieved by short rest: less than 5 min and no postural changes necessary
  3. reproducible: same distance or time to elicit pain, same location of pain, same amount of rest to relieve pain
     - the presence of the preceding features differentiates vascular claudication from neurogenic claudication or MSK pain
- critical limb ischemia (CLI):
  1. includes rest pain, night pain, tissue loss (ulceration or gangrene)
  2. pain most commonly over the forefoot/toes, waking person from sleep, and often relieved by hanging foot off bed
  3. ankle pressure <40 mmHg, toe pressure <30 mmHg, ABI <0.40
     - distal pulses are absent, bruits may be present
     - signs of poor perfusion: hair loss, hypertrophic nails, atrophic muscle, ulcerations and infections, slow capillary refill, prolonged pallor with elevation and rubor on dependency, and venous troughing (Buerger's sign/Buerger's angle) (collapse of superficial veins of foot)
  4. high risk of 1 yr limb amputation and mortality

### Investigations
- routine blood work, fasting metabolic profile
- ABI: highest ankle pressure (dorsalis pedis or posterior tibial) for each side divided by highest brachial pressure (see Table 2 for Cut-Offs)
- arterial duplex ultrasound: combines traditional and Doppler ultrasound to visualize blood vessels and characterize flow and plaques
- non-invasive: CTA and MRA excellent for large arteries (aorta, iliac, femoral, popliteal) but may have difficulty with tibial arteries (especially in the presence of disease)
  - require IV injection of nephrotoxic contrast (iodinated contrast for CTA, gadolinium for MRA)
  - used primarily for planning interventions
- invasive: arteriography
  - superior resolution to CTA/MRA, better for tibial arteries, can be done intraoperatively as part of intervention
  - can be diagnostics and/or therapeutic



**Distinction between Critical Limb Ischemia (CLI) and Acute Limb Ischemia (ALI)**

**ALI:** A precipitous decrease and/or cessation in blood flow to a limb threatening viability. Typically, due to arterial embolism or thrombosis, or other acute cause. Characterized by rapidly worsening leg pain that present for <2 weeks (usually hours to days) in patients with no history of claudication

**CLI:** Severe manifestation of PAD where blood flow to the extremities is markedly reduced. Defined as ischemic foot pain at rest or at night, occurring >2 weeks, wounds, or gangrene in patients with a known history of claudication



**Leriche Syndrome**
Chronic aortoiliac occlusive disease presenting with a triad of:
1. Claudication (of buttocks and thighs)
2. Decreased femoral pulses
3. Impotence



**Subclavian Steal Syndrome**
A chronic arterial disease of the upper limb where stenosis or occlusion of the proximal subclavian artery results in retrograde flow from the vertebral artery, compromising vertebrobasilar circulation. Patients can present with pre/syncope and neurological deficits especially upon exertion of the limb

**Table 2. Ankle-Brachial Index Cut-Offs**

| ABI Recording | Degree of Ischemia |
|---|---|
| >1.40 | Suspect wall calcification (common in diabetes) |
| 0.91 - 1.40 | Normal |
| 0.70 - 0.90 | Mild |
| 0.40 - 0.69 | Moderate |
| <0.40 | Severe |

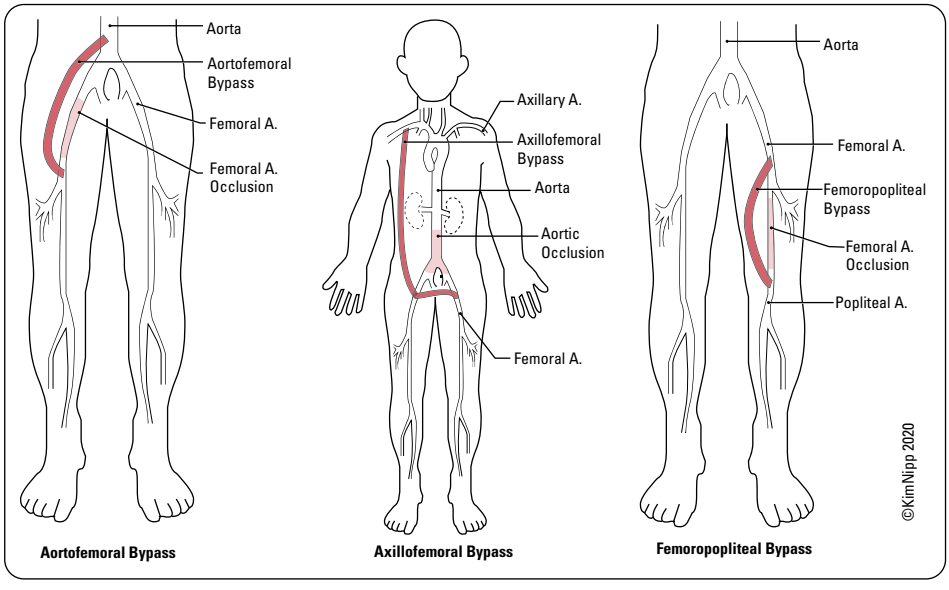



**Figure 2. Aortofemoral bypass, axillofemoral bypass, and femoropopliteal bypass**

## Treatment

- goals
  - preserve viability (save the leg)
  - preserve life (avoid complicated procedures in sick patients)
  - improve function and alleviate symptoms
  - prevent deterioration and recurrence
- conservative
  - risk factor modification (smoking cessation, glucose control, treatment of HTN and hyperlipidemia)
  - structured exercise program (30-45 min 3x/wk): improves collateral circulation and muscle oxygenation
  - foot care (especially in DM): trim toenails, check between toes for skin breaks, wear socks and shoes, clear shoes of any debris, keep wounds clean/dry, avoid trauma and pressure on wounds
- pharmacotherapy
  - for global cardiovascular protection since patients with PAD are at increased risk for CAD and CVD
  - antiplatelet agents (e.g. aspirin, clopidogrel)
  - statin
  - ACEI/ARB
- surgical
  - indications: severe lifestyle impairment, vocational impairment, critical ischemia
  - revascularization
    - endovascular (angioplasty ± stenting)
    - endarterectomy: removal of plaque and repair with patch (usually distal aorta or common/deep femoral)
    - bypass graft sites: aortofemoral, axillofemoral, femoropopliteal, femoro-tibial, femorofemoral bypass
    - graft choices: saphenous vein graft (reversed or *in situ*), synthetic [polytetrafluoroethylene graft (e.g. Gore-Tex® or Dacron®)]
- amputation: if not anatomically suitable for revascularization, persistent serious infections/gangrene, unremitting rest pain that is poorly controlled with analgesics, medically unfit for revascularization

## Prognosis

- claudication: conservative therapy: 60-80% improve, 20-30% stay the same, 5-10% deteriorate, 5% will require intervention within 5 yr, <4% will require amputation
- for patients with critical limb ischemia, at 1 yr: 25% risk of mortality (secondary to CVA/MI), 25% risk of amputation, 50% alive with two limbs, 33% 5 yr survival rate

**Differential Diagnosis of Lower Extremity Pain**

**Vascular**
- Atherosclerotic disease
- Fibromuscular dysplasia
- Popliteal entrapment syndrome
- Venous claudication/hypertension

**Neurogenic**
- Neurospinal disease (e.g. spinal stenosis)
- Complex regional pain syndrome
- Radiculopathies
- Diabetic neuropathy

**MSK**
- Osteoarthritis
- Rheumatoid arthritis/connective tissue disease
- Remote trauma

**Treating PAD**

Note that symptoms do not necessarily correlate with ABI measurement. For example, a patient with ABI of 0.45 may be asymptomatic. Intervention is guided by both ABI measurements and symptoms

**The ABCDEs of PAD Treatment**

A **Anti-plt** (ASA, plavix), anti-coagulant (if indicated), **ACEI/ARB**
B Blood pressure control; target sBP <140, β-blocker (if indicated)
C Cholesterol management (**statin**); target LDL <2, smoking cessation
D Diabetic control; target HbA1c <7%, Diet/weight management
E Exercise (3x/wk, 20 min per session)

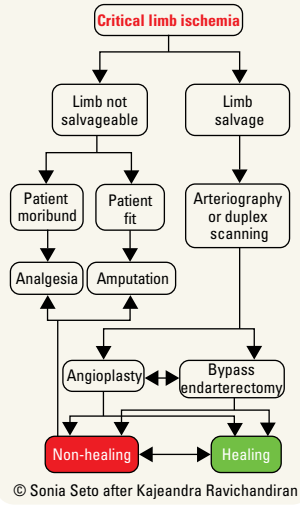



**Figure 3. Treatment options for CLI**
Modified from Beard JD. Chronic lower limb ischemia. *BMJ* 2000;320:854-857

# Aortic Disease

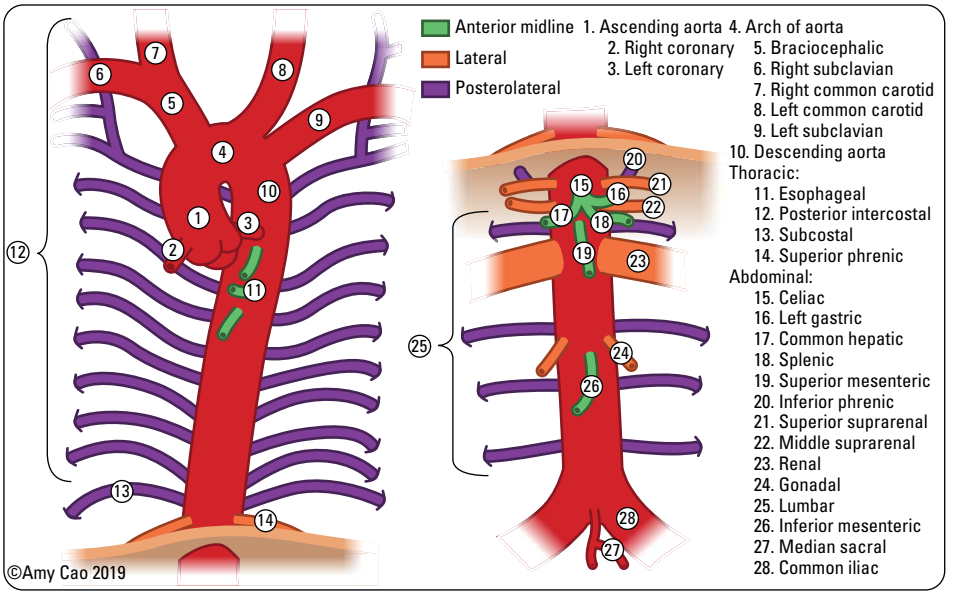



**Figure 4. Aortic anatomy**

## Aortic Dissection

### Definition
- tear in aortic intima allowing blood to dissect into the media
- Stanford classification: Type A (involve the ascending aorta) vs. Type B (distal to left subclavian artery)
- acute <2 wk (initial mortality 1% per hour for Type A dissections)
- chronic >2 wk

### Etiology
- most common: HTN
- other: connective tissue disease (e.g. Marfan's, Ehlers-Danlos type IV), cystic medial necrosis, atherosclerosis, congenital conditions (e.g. coarctation of aorta, bicuspid aortic valves, patent ductus arteriosus), infection (e.g. syphilis), trauma, arteritis (e.g. Takayasu's)

### Epidemiology
- M:F = 3:1
- small increased incidence in African-Canadians (related to higher incidence of HTN); lowest incidence in Asians
- peak incidence 50-65 yr old; 20-40 yr old with connective tissue diseases

### Clinical Features
- sudden onset tearing chest or back pain that radiates distally or between the scapulae with:
  - HTN
  - ischemic syndromes due to occlusion of aortic branches: coronary (MI), carotids (ischemic stroke, partial Horner's syndrome), splanchnic (mesenteric ischemia), renal (AKI), peripheral (ischemic leg), intercostal vessels (spinal cord ischemia)
  - "unseating" of aortic valve cusps (new diastolic murmur in 20-30%) in Type A dissection
  - rupture into pleura (dyspnea, hemoptysis) or retroperitoneum (hypotension, shock) or pericardium (cardiac tamponade in Type A dissection)
  - syncope

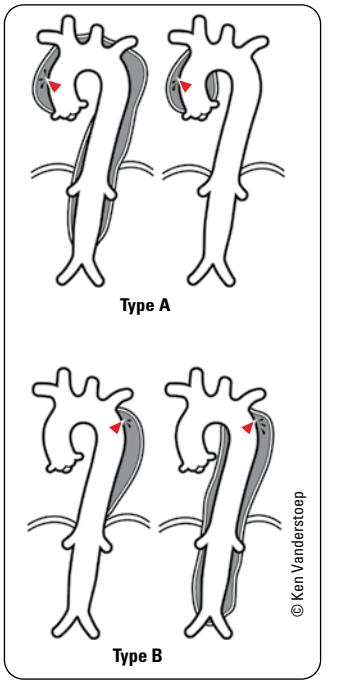



**Figure 5. Stanford classification of aortic dissection**

### Investigations
- CTA is the mainstay for both diagnosis and determining the type and extent of dissection
- ECG to rule out cardiac causes: LVH ± ischemic changes, pericarditis, heart block, MI
- CXR: widened mediastinum, hemothorax if ruptured, apical pleural cap
- TEE: can visualize aortic valve and thoracic aorta but not abdominal aorta; rule out intra-cardiac thrombus
- consider: lactate (elevated in ischemic gut, shock), amylase (rule out pancreatitis), troponin (rule out MI), CBC, electrolytes, Cr (renal failure), LFTs (shock, liver)

### Treatment

- Type A dissection needs referral to cardiac surgeon for urgent repair
  - resection of segment with intimal tear; reconstitution of flow through true lumen; replacement of the affected aorta with prosthetic graft
  - post-operative complications: renal failure, intestinal ischemia, stroke, paraplegia, persistent leg ischemia, death
  - 2/3 of patients die of operative or post-operative complications
  - initial mortality rate without surgery is 1% per h for first 24 h, 30% 1 wk, 80% 2 wk
- Type B dissection is usually managed medically in the absence of spinal/mesenteric/limb malperfusion syndrome
  - <10-20% require urgent operation for complications
  - acute therapy is typically with intravenous antihypertensives titrated to sBP of 100-120 mmHg measured by arterial line and HR of 50-65 bpm in critical care setting
  - may transition to oral meds after initial control
  - α and β-blocker to lower BP and decrease cardiac contractility (e.g. labetalol); nondihydropyridine CCB if clear contraindications to β-blockers, and as second line therapy; IV nitroglycerin also used as second line agent
  - ACEI and/or other vasodilators if insufficient BP or HR control
  - selective intervention (endovascular or surgical) for complications or refractory symptoms/ progression despite medical therapy
  - may be a subset of patients who could be well treated with early aortic stent-grafting after initial medical stabilization
  - with treatment, 60% 5 yr survival, 40% 10 yr survival
  - long term complications include aneurysmal degeneration of the aorta

## Aortic Aneurysm

### Definition

- localized dilatation of an artery >1.5x normal diameter (3 cm and larger for abdominal aorta)
- true aneurysm: involves all vessel wall layers (intima, media, adventitia)
- false aneurysm (psuedo-aneurysm): does not involve all layers; breach in intima/media that allows blood to collect between media and adventitia
- aneurysms can rupture, thrombose, embolize, erode, and fistulize

### Classification

- shape
  - fusiform: concentric; involves full circumference of vessel wall
  - saccular: eccentric; involves only a portion of vessel wall (theoretical higher risk of rupture due to unequal distribution of pressure)
- location
  - thoracic aortic aneurysm (TAA): ascending, transverse arch, descending
  - thoracoabdominal
  - abdominal aortic aneurysm (AAA): 90-98% are infrarenal
    - suprarenal: starts above the renal arteries but does not involve the thoracic aorta
    - pararenal: starts at the renal arteries but the SMA origin is not aneurysmal
    - juxtarenal: starts immediately distal to renal arteries (there is no normal aorta immediately distal to the origin of the renal arteries); renal artery origin is not aneurysmal
    - infrarenal: starts distal to the renal arteries (there is some normal aorta immediately distal to the origin of the renal arteries)

### Etiology and Risk Factors

- risk factors: smoking (current or prior), advanced age, male sex, Caucasian race, FMHx, presence of other large vessel aneurysms, HTN
- degenerative
- traumatic
- mycotic (*Salmonella, Staphylococcus*, usually suprarenal aneurysms)
- connective tissue disorder (Marfan syndrome, Loeys-Dietz Syndrome, Ehlers-Danlos type IV syndrome)
- vasculitis
- infectious (syphilis, fungal)
- ascending thoracic aneurysms are associated with bicuspid aortic valve
- aortic dissection
- congenital (i.e. Turner's syndrome)

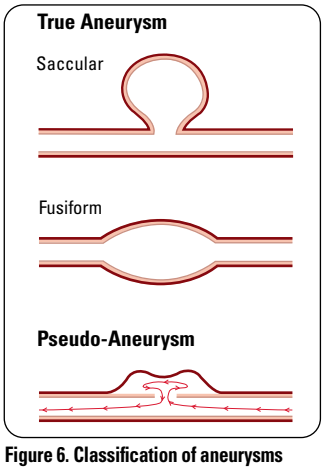



**Figure 6. Classification of aneurysms**

**Classic Triad**

- Hypotension/collapse
- Back/abdominal pain
- Palpable, pulsatile abdominal mass (caution in patients with raised BMI)

**Initial Management**

- Intravenous access with two peripheral large bore IVs
- Permissive hypotension (sBP target 70-90 mmHg or enough to maintain mental status)

## Clinical Features

- 75% asymptomatic
- most commonly in the abdominal aorta
- common presentation: due to acute expansion or rupture
  - syncope
  - pain (chest, abdominal, flank, back)
  - hypotension
  - palpable pulsatile mass above the umbilicus
  - airway or esophageal obstruction, hoarseness (left recurrent laryngeal nerve paralysis), hemoptysis, or hematemesis (indicates thoracic or thoracoabdominal aortic aneurysm)
  - distal pulses may be intact

**Canadian Society of Vascular Surgery 2018 AAA Screening Guidelines Recommend:**

- One time screening ultrasound for:
  - Men 65-80
  - Women 65-80 with smoking history or cardiovascular disease
  - First degree relatives after 55
- Repeat ultrasound 10 years after initial screening if aortic diameter >2.4 cm and <3 cm

## Investigations

- blood work: CBC, electrolytes, urea, creatinine, PTT, INR, blood type and crossmatch
- abdominal U/S (approaching 100% sensitivity, up to ± 0.6 cm accuracy in size determination) – useful for screening and surveillance
- CT with contrast (accurate anatomic visualization, size determination, EVAR planning)
- peripheral arterial duplex (rule out aneurysms elsewhere, e.g. popliteal)

## Treatment

- conservative (for asymptomatic aneurysms that do not meet the size threshold for repair; see below)
  - cardiovascular risk factor reduction: smoking cessation; control of HTN, DM, hyperlipidemia, regular exercise, watchful waiting, U/S surveillance with frequency depending on size and location
- surgical
  - indications
    - ruptured
    - symptomatic (tenderness on palpation of the aneurysm)
    - AAA: size >5.5 cm (men) or >5.0 cm (women)
  - risk of rupture depends on: size, family history of rupture, rate of enlargement (>1 cm/yr in diameter), symptoms, and comorbidities (HTN, COPD, dissection), smoking
  - elective AAA repair mortality 2-5% for open repair (1-2% for EVAR); elective TAA repair mortality <10% (highest with proximal aortic and thoracoabdominal repairs)
  - surgical options
    - open surgery (laparotomy or retroperitoneal) with graft replacement
      - complications
        - early: renal failure, spinal cord injury (paraparesis or paraplegia), impotence, arterial thrombosis, anastomotic rupture or bleeding, peripheral emboli
        - late: graft infection/thrombosis, aortoenteric fistula, anastomotic (pseudo) aneurysm
        - death
    - endovascular aneurysm repair (EVAR)
      - newer procedure
      - advantages: preferred to open surgery in higher risk patients with suitable anatomy; decreased perioperative morbidity and mortality, procedure time, need for transfusion, ICU admissions, length of hospitalization, and recovery time
      - disadvantages: endoleak rates as high as 20-30%, device failure increasing as longer follow-up periods are achieved, re-intervention rates 10-30%, cost-effectiveness is an issue, radiation exposure (especially in younger patients due to need for life-long follow-up)
      - complications
        - early: immediate conversion to open repair (<1%), groin hematoma, arterial thrombosis, iliac artery rupture and thromboemboli, renal failure, impotence
        - late: endoleak, graft kinking, fracture and migration, thrombosis, rupture of aneurysm, complications of radiation exposure
        - death

# Carotid Stenosis

## Definition
- narrowing of the internal carotid artery lumen due to atherosclerotic plaque formation, usually near common carotid bifurcation into internal and external carotids (carotid bulb)

## Risk Factors
- HTN, smoking, DM, CVD or CAD, dyslipidemia, older age

## Clinical Features
- may be asymptomatic
- if symptomatic – TIA, ischemic stroke; may be hemispheric presentation (deficits contralateral to carotid lesion) or ocular presentation (deficits ipsilateral to carotid lesion – amaurosis fugax or retinal artery stroke)
- physical exam
  - auscultation over carotid bifurcation for bruits (does not correlate with degree of stenosis)
  - fundoscopy: cholesterol emboli in retinal vessels (Hollenhorst plaques)

## Investigations
- CBC, PT/INR, PTT (hypercoagulable states)
- ECG, Echo (rule out other causes of stroke)
- carotid duplex U/S: determines severity of disease (mild/moderate/severe stenosis or occlusion)
- angiography: CTA, MRA, conventional cerebral angiography

## Treatment
- generally the decision to treat with best medical therapy (BMT) alone vs. BMT + surgical management depends on whether stenosis is asymptomatic or symptomatic (see Table 3); size of infarct, patient functional recovery, life expectancy and comorbidities are important in decision-making
- >50% symptomatic stenosis is defined as stroke or TIA within the past 6 mo; ideally surgical treatment should be done within the first 2 weeks of symptom onset
- lifestyle modifications: smoking cessation, weight loss, dietary changes

**1. medical management**
- anti-hyperglycemics: if concomitant diabetes
- anti-hypertensives: ACEI/ARB particularly if concomitant CHF or renal disease
- statins: aggressive management to achieve LDL-C reduction; plaque stabilization effect
- anti-platelet agents (ASA ± Clopidogrel): confer ~25% relative risk reduction

**2. surgical management**
- carotid endarterectomy (CEA) or carotid artery stenting (CAS) for symptomatic carotid stenosis: choosing one over the other is controversial - if stroke prevention is the primary outcome, CEA has lower risk
- CEA – generally mainstay of treatment
- CAS – indicated if poor surgical access, radiation-induced stenosis, or comorbidities that increase risk of surgery/anesthesia
- aggregate risk of death, stroke, or MI in periprocedural period is not significantly different between CEA or CAS
  - higher risk of periprocedural stroke in CAS
  - higher risk of MI and temporary cranial nerve palsy in CEA

**Table 3. Indications for Medical vs. Surgical Management of Carotid Stenosis**

| Stenosis | Asymptomatic | Symptomatic |
|---|---|---|
| <50% | Best Medical Therapy | Best Medical Therapy |
| 50-60% | Best Medical Therapy | |
| 60-70% | Best Medical Therapy<br>+<br>Surgical management if:<br>• Progression of disease<br>• Young and otherwise healthy<br>• Ocular ischemic syndrome<br>• Life expectancy >5 y<br>• Surgeon's perioperative morbidity/mortality risk <3%<br><br>60-99% stenosis: ARR = 1 - 3%; NNT = ~33 | Best Medical Therapy<br>+<br>Surgical management if:<br>Surgeon's perioperative morbidity/mortality risk <3%<br><br>50-70% stenosis: ARR=4.6%, NNT=22 |
| 70-99% | Surgical management if:<br>Surgeon's perioperative morbidity/mortality risk <3%<br>ARR = 1-3%; NNT ~ 33 | Surgical management if:<br>Surgeon's perioperative morbidity/mortality risk <3%<br>ARR = 16%; NNT ~ 6 |
| 100% | Best Medical Therapy<br>No surgical intervention | Best Medical Therapy<br>No surgical intervention |

ARR = absolute risk reduction; NNT = number needed to treat

**10-Year Stroke Prevention after Successful Carotid Endarterectomy for Asymptomatic Stenosis (Acts-1): A Multicentre Randomised Trial**
Lancet 2010;376:1074-1084
**Study**: Asymptomatic Carotid Surgery Trial (ACST), a RCT with follow-up at 10 yr.
**Patients**: 3120 asymptomatic patients with significant carotid artery stenosis (126 centres in 30 countries) were randomized equally between immediate carotid endarterectomy (CEA) and indefinite deferral of CEA and were followed for up until death or to a median of 9 yr among survivors (IRQ 6-11).
**Main Outcome**: Perioperative mortality and morbidity (death or stroke within 30 d) and non-perioperative stroke
**Conclusions**: In asymptomatic patients under age 75 with significant carotid artery stenosis, successful CEA reduces the 10-yr stroke risk. Net benefit depends on risks from unoperated carotid lesions, future surgical risks, and whether life expectancy exceeds 10 yr.

# Peripheral Venous Disease

## Venous Thromboembolism

• see Hematology, H35

## Chronic Venous Insufficiency

### Definition
• wide spectrum of chronic venous disease with advancing symptoms of edema, skin changes, varicosities or leg ulcers

### Epidemiology
• primary venous insufficiency is the most common venous disorder of lower extremity
• 65% of North American adult population develops some degree of venous insufficiency

### Etiology
• spectrum of chronic venous disease involving deep and superficial lower extremity veins caused by calf muscle pump dysfunction, venous obstruction, and chronic valvular incompetence (reflux) due to phlebitis, varicosities or DVT
• final common pathway is development of venous hypertension, leading to histologic and physiologic inflammatory changes
• primary (99% of cases) venous insufficiency: venous valve incompetence or obstruction
  ▪ suspected risk factors: increasing age, systemic hormonal contraceptive use, prolonged standing, pregnancy, obesity
• secondary venous insufficiency: DVT, malignant pelvic tumours with venous compression, congenital anomalies, arteriovenous fistulae, trauma

### Clinical Features and Complications
• pain (most common) described as fullness/tightness and aching; worst at end of the day
• ankle and calf edema; relieved by foot elevation
• pruritus, eczema, burning, aching, fullness/tightness, nocturnal cramping
• stasis dermatitis, brownish hyperpigmentation (hemosiderin deposits), subcutaneous fibrosis if chronic (lipodermatosclerosis)
• ulceration: shallow, above medial malleolus (gaiter area), weeping (wet), painless, irregular outline
• varicose veins: visible, long, dilated and tortuous superficial veins (great or small saphenous veins and tributaries) resulting from incompetent valves in the deep, superficial, or perforator systems;
• signs of recurrent superficial thrombophlebitis and DVT
• bleeding or hematoma of varicosities secondary to trauma

### Investigations
• ABI (pre-compression to ensure no arterial disease)
• venous duplex U/S

### Treatment
• conservative
  ▪ elastic compression stockings, ambulation, periodic rest-elevation, avoid prolonged standing
  ▪ ulcers: wound care using multilayer compression bandage ± antibiotics ± debridement prn
  ▪ medical treatments are variable e.g. pentoxifylline, horse chestnut oils, etc
• surgical
  ▪ surgical excision: destruction of vein with partial or complete removal; techniques include vein ligation/stripping, phlebectomy, perforator ligation
• indications for surgery: failure of conservative treatment, symptomatic varix (pain, bleeding, recurrent thrombophlebitis), tissue changes (hyperpigmentation, ulceration), cosmetic
• 10 year post-operative recurrence of 20%
• endovenous: laser therapy, radiofrequency ablation (RFA), foam/liquid/glue sclerotherapy



**May-Thurner Syndrome**
In affected individuals the right common iliac artery compresses the left common iliac vein, resulting in venous congestion and possible DVT of the left leg
Consider in patients presenting with left leg thrombosis and no clear underlying hypercoagulability

# Lymphedema

## Definition
- impaired lymphatic drainage resulting in accumulation of interstitial fluid and fibroadipose tissue

## Etiology
- primary
  - congenital lymphedema (e.g. Milroy disease): presents <2 yr old
  - lymphedema praecox (75% of primary cases): presents in adolescence at onset of puberty
  - lymphedema tarda: presents >35 yr old
- secondary
  - infection: **filariasis** (#1 cause worldwide), cellulitis, lymphadenitis, tuberculosis
  - inflammation: rheumatoid arthritis, dermatitis, psoriasis, sarcoidosis
  - endocrine: pre-tibial myxedema
  - malignant infiltration: axillary, groin or intrapelvic, pressure from large tumours
  - trauma and tissue damage: **radiation/surgery (axillary, groin lymphadenectomy)** (#1 cause in North America), burns, vein surgery, scarring
  - venous disease: chronic venous insufficiency, venous ulcer, post-thrombotic syndrome

## Clinical Features
- classically non-pitting edema and hyperkeratotic cutaneous/subcutaneous changes with progressive disease
- impaired limb mobility, discomfort/pain, psychological distress
- positive Stemmer sign (sensitive): examiner unable to lift skin of thickened skin fold at the base of second toe or finger
- lipodermatosclerosis
- ulcerations

## Investigations
- lymphoscintigraphy: most definitive test
- secondary causes of lymphedema must be evaluated and treated appropriately if found

## Treatment
- avoid limb injury (can precipitate or worsen lymphedema)
- cellulitis/erysipelas: treat early to avoid further lymphatic damage
- skin hygiene
  - daily skin care with moisturizers
  - early medical assessment and treatment for infection (topical for fungal infection; systemic for bacterial infection)
- external support: intensive (compression bandages) vs. maintenance (compression garments)
- exercise: gentle daily exercise of affected limb, gradually increasing ROM (must wear compression garment while exercising)
- massage: manual lymph drainage therapy
- surgical: physiological (early disease, increase lymphatic drainage) vs. reductive (advanced disease, remove fibroadipose deposits)

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